Peer Review File
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Reviewer A

Comment 1: If the term Oncoplastic breast surgery was first used in 1993, why performing a review from 1985?
Reply 1: We have included in the search the period from the beginning of publications on breast-conserving surgery (1985) to assess its evolution, focusing subsequently on the most recent publications in which oncoplastic surgery is mentioned within breast-conserving surgery.
Changes in the text: None.

Comment 2: Mention that it is not going to be possible to have RCT with O-BCS compared to mastectomy or S-BCS
Reply 2: We agree with the comment.
Changes in the text: We added some data (see page 5, line 113-116): It is challenging to conduct an RCT comparing breast-conserving surgery with oncoplasty (O-BCS) to mastectomy or standard breast-conserving surgery (S-BCS), given ethical considerations, patient preferences, clinical variability, and changing contexts in medical practice.

Comment 3: I understand that S-BCS is standard breast conservative surgery….it is first mentioned in line 99…nos clarified as O-BCS is explained in line 66
Reply 3: We agree with the comment.
Changes in the text: We added some data (see page 3, line 63-64): At a similar onset of the standard breast conserving surgery (S-BCS), the term oncoplastic breast surgery (O-BCS) was firstly used…

Comment 4: They mention different methods for per-surgical localization but actually talking only about wires, seeds or IOUS seems like a low level of definition as there are many different seeds and also another methods not mentioned
Reply 4: We agree with the comment
Changes in the text: We added some data (see page 7, line 139-146): The pre-surgical localization of lesions is a crucial point, and if necessary, employing multiple techniques or multiple markers to delineate the area for resection. Wire guided localization (WGL) is the most common used localization method, and it is considered the standard localization method of non-palpable breast lesions. Notwithstanding, newer technologies have emerged that enable the localization of lesions with a similar detection rate and clear margins, enhancing the experiences for both the surgeon and the patient. These include radio-guided occult lesions localization (ROLL), intraoperative ultrasound, seeds (Radioactive Seed, MagSeed®, SAVI Scout®), among others.

Comment 5: They don't mention what they understand as a clear margin…no ink on tumour? 1 mm? 2 mm?
Reply 5: We have taken into account the margins recommended by international guidelines; we have included the information.
Changes in the text: We added some data (page 8, lines 180-183): "Negative margins" is currently considered as no ink on the tumor when we are referring to infiltrating breast carcinoma, as indicated by the NCCN guidelines. However, distinctions arise in cases of ductal carcinoma in situ (DCIS), where margins of at least 2 mm are linked to a decreased risk of ipsilateral breast tumor recurrence.

Comment 6: Differences of results between the different options to assess intraoperatively margin status…which is best in the literature?
Reply 6: We searched the literature and added the following information
Changes in the text: Page 7, lines 159-178. The most well-established methods for margin assessment include gross inspection, frozen section analysis, and imprint cytology. According to one systematic review, frozen section analysis (FSA) and imprint cytology (IC) could reduce

reoperation rates from 35% to 10% and 11%, respectively.
Radiological methods have shown promising results, with numerous studies unanimously demonstrating the excellence of intraoperative ultrasound (IOUS) in achieving negative margins, reducing resection tissue volume, and improving overall aesthetic results and patient satisfaction. Regarding the use of mammography, the reported sensitivity of specimen mammography for intraoperative margin assessment ranged from 20.6% to 45.45%. According to the authors, mammography would be highly useful in cases that radiologically present as microcalcifications. An emerging trend involves the participation of artificial intelligence (AI) during image identification. Novel techniques provide alternative approaches to evaluating margins during surgery and include radiofrequency spectroscopy, bio-impedance spectroscopy, and optical coherence tomography (OCT). There are also preliminary studies involving the use of drugs to modify and make lesions visible, such as studies including EC17 and Trastuzumab, or 18F-FDG used for specimen PET-CT.
Nevertheless, BCS for DCIS and BCS after neo-adjuvant chemotherapy pose significant challenges in achieving negative margins.

Comment 7: If they mention in lines 192-193 the LICAP and TDAP they should also have to mention the rest of the CWPF. AICAP, MICAP and LICAP
Reply 7: We agree with the comment
Changes in the text: We added some data (Pag 10, lines 231-235)…or volume replacement procedures, including autologous flaps designed to reconstruct a new breast after resection, such as chest wall perforator flaps (CWPF), among which are the Lateral Intercostal Artery Perforator (LICAP), Lateral Thoracic Artery Perforator (LTAP), a combined flap, and Anterior Intercostal Artery Perforator/Medial Intercostal Artery Perforator (AICAP)/(MICAP).

Comment 8: Related to contralateral symmetrization something should be said about theatres availability…in some countries that lack of theatres and staff precludes it
Reply 8: We agree with the comment
Changes in the text: We added some data (Page 11-12, lines 257-261): In this context, it is relevant to address the availability of operating theaters, as this surgical intervention aims to achieve aesthetic symmetry. In some countries, there is a significant limitation in terms of access to operating theaters and adequately trained medical staff, which can prevent or hinder the execution of contralateral symmetrization procedures.

Reviewer B
Comment 9: Appreciate review of various aspects of oncoplastic breast surgery. With that limited search terms of two, how confident are you that important articles in Oncoplastic Breast Surgery is not missed and reviewed. Difficult review to be carried out to assess a meaningful subset analysis due to the heterogeniety of the procedures and techniques used in varion studies.
Reply 9: The choice to use only the terms "Oncoplastic surgery" and "breast conservative surgery" in a literature review could be justified for several reasons. These two terms are broad and encompass a variety of articles related to oncoplastic surgery and breast conservative surgery.
"Oncoplastic surgery" is a term that includes various surgical techniques used in oncoplastic breast surgery. Combined with "breast conservative surgery," which refers to a broader category including various breast-conserving interventions, a comprehensive review addressing multiple aspects could be achieved. By narrowing the search to these general terms, a wide spectrum of research and reviews in the field could be captured, making the process clearer and more manageable. The selection of these terms aligns with the specific objectives of the review and the research question.
Changes in the text: None.

Reviewer C
Comment 10: I read with interest your manuscript titled "Evolution of breast conserving surgery. Current implementation of oncoplastic techniques in breast conserving surgery: a literature

review.". The study provides a comprehensive overview of recent findings in the O-BCS field.
In my opinion the study covers interesting topics and is well structured.
Reply 10: I sincerely appreciate your positive opinion about our study. We are pleased to know that the work has been perceived as a comprehensive overview of recent findings in the field of breast-conserving surgery with oncoplastic techniques. Additionally, we are thankful that you found the study to cover interesting topics and to be well-structured.
Changes in the text: None.

Reviewer D

Comment 11: The authors dedicate one results chapter to margin status. I would suggest to add the re-excision-rate as this outcome may correct for changes in the definition of R1-resections for carcinomas in 2014 (J Clin Oncol. 2014 May 10;32(14):1507-15. doi: 10.1200/JCO.2013.53.3935. Epub 2014 Feb 10.) and for DCIS in 2016 (J Clin Oncol. 2016 Nov 20;34(33):4040-4046. doi: 10.1200/JCO.2016.68.3573. Epub 2016 Oct 31). In this context I would suggest to incorporate the findings of the retrospective, multicenter OPBC-01/iTOP2 study in your discussion (Ann Surg Oncol. 2022 Feb;29(2):1061-1070. doi: 10.1245/s10434-021-10809-1. Epub 2021 Oct 13.).
Reply 11: We included these references
Changes in the text: We added some data (page 8-9, lines 180-187): "Negative margins" is currently considered as no ink on the tumor when we are referring to infiltrating breast carcinoma, as indicated by the NCCN guidelines (10). However, distinctions arise in cases of ductal carcinoma in situ (DCIS), where margins of at least 2 mm are linked to a decreased risk of ipsilateral breast tumor recurrence (20). While Oncoplastic level II resections in high-risk breast cancer patients enhance margin width, they do not correlate with lower rates of local recurrence. Interestingly, the use of oncoplastic level II techniques significantly reduces the number of re-excisions attributed to R1 (21).

Comment 12: For the rate of positive margins after OBCS please also refer to the systematic review by De la Cruz showing R1-rates of 0-16% (Ann Surg Oncol. 2016; 23: 3247-3258 https://doi.org/10.1245/s10434-016-5313-1).
Reply 12: We included this reference
Changes in the text: Page 9, Line 188-192. In De la Cruz's systematic review, the rate of positive margins in oncoplastic surgery varied widely (0 - 39.7%), given that the assessment of positive margins is highly heterogeneous. Eleven studies reported specific margins for 1455 patients. Among these patients, 143 (9.8%) were classified as having positive margins, of which 113 (7.8%) had ink on the tumor.

Comment 13: Please state, whether there are any ongoing trials prospectively assessing oncoplastic surgery compared to non-oncoplastic techniques. One would be the COSMAM trial (BMC Cancer. 2018;18:456).
Reply 13: We included this reference
Changes in the text: Page 16, lines 356-358. Currently, the COSMAM study is being conducted at a single-center in the Netherlands. This prospective study aims to evaluate the quality of life and cosmetic outcomes in patients undergoing standard lumpectomy versus level I or II OBCS.

Comment 14: In your paragraph on lesion localization please mention the currently ongoing EUBREAST MELODY study (Cancers (Basel). 2023 Feb 12;15(4):1173. doi: 10.3390/cancers15041173.)
Reply 14: We included this reference
Changes in the text: Page 7, lines 147-151. We added some data (Page 6-7, lines 136-140): In this context, the ongoing EUBREAST MELODY study aims to assess different imaging-guided localization methods in terms of oncological safety, patient-reported outcomes, and satisfaction levels among surgeons and radiologists. The target accrual is 7,416 patients, with enrollment starting in January 2023. The study will be conducted across 20 countries.

Comment 15: In line 217 the authors state that patients being given the option to proceed with immediate contralateral symmetrization compared to a staged approach, most opt for an immediate symmetrization. From my personal experience I can not confirm the authors statement. Therefore, I would suggest to rephrase this sentence to state that in your clinical practice your experience shows that patients rather choose a one-stage procedure. Or to erase this sentence.
Reply 15: I agree with the previous comment; it is a subjective observation.
Changes in the text: I erased this sentence

Comment 16: In the chapter on complications the authors state that wound dehiscence is associated with technical flaws. Whilst this statement may be true, patient-related risk-factors have been shown to be a major influence factor on wound healing, stressing the need for careful patient selection. Please adapt this sentence (Plast Reconstr surgery Glob open. 2018;6:e1732; https://journals.lww.com/annalsofsurgery/fulltext/2012/03000/high_body_mass_index_and_smoking_predict_morbidity.23.aspx. 2012). Furthermore, high-volume oncoplastic breast-conserving surgery was recently shown to be an independent risk-factor for delayed wound healing (Eur J Surg Oncol. 2023 Oct;49(10):107032. doi: 10.1016/j.ejso.2023.107032. Epub 2023 Aug 16).
Reply 16: We included these reference
Changes in the text: Page 13, Line 283-289. Fat necrosis and wound dehiscence, ranging from 0.9% to 6%, are uncommon yet challenging complications of oncoplastic procedures. It is important to emphasize that while these issues are indeed associated with technical flaws, patient-related risk factors have been identified as significant influences on wound healing, underscoring the necessity for careful patient selection. This consideration aligns with findings demonstrating that high-volume oncoplastic breast-conserving surgery is an independent risk factor for delayed wound healing

Comment 17: Please include a statement on possible adjuvant treatment delays due to complications after O-BCS as assessed in the Cochrane Review by Nanda et al. (DOI: 10.1002/14651858.CD013658.pub2).
Reply 17: We included these reference
Changes in the text: Page 13, lines 303-307. The Cochrane review by Nanda suggests that the time to adjuvant therapy may be increased, specifically in the case of adjuvant radiotherapy, when utilizing O-BCS as opposed to S-BCS. This potential extension in time could be attributed to delays arising from complications. The delay in adjuvant radiotherapy is estimated to range between 7.21 and 12.1 days, which could hold clinical significance.

Comment 18: In the section on QoL please note that whilst studies comparing S-BCS to O-BCS, as well as studies comparing S-BCS to oncoplastic surgery exist, evidence is needed to assess whether high-volume oncoplastic breast conserving surgery (including a higher risk of complications yet a potentially lower rate of re-excisions) may impact QoL.
Reply 18: It's a good observation, we'll include it.
Changes in the text: Page 15, lines 339-341. Evidence is required to assess whether high-volume oncoplastic breast-conserving surgery, which entails a heightened risk of complications but potentially a lower rate of re-excisions, may impact quality of life (QoL).

Comment 19: Please provide evidence (reference) for your paragraph starting at line 516, or emphasize that this is your personal experience, or erase the paragraph.
Reply 19: The paragraph starting at line 516 is: E.M. conceived of the presented idea. I.T. and I.C. carried out the bibliography review and wrote the manuscript in consultation with E.M. and H.C. E.M. All authors discussed the final manuscript.
Changes in the text: None.

Minor remarks
Please include the month of inclusion of literature in 1985 – I assume January?
Yes, January

Reference #74 seems to be erroneous.
Urban, C.D., Anselmi, K.F., Kuroda, F., & Schwartz, J. Oncoplasty as the Standard of Care in Breast Cancer Surgery. European Oncology and Haematology, 2014, 10, 43

Please subject the manuscript to English proof-reading and editing.

Reviewer E

There is a dearth of high-quality literature relating to oncoplastic breast surgery (OBCS) with much heterogeneity within patient populations that leads to confounding and challenges with interpretation of data. In particular, there are few randomized controlled trials in this field that might otherwise provide robust evidence for the superiority of one procedure over another. More recently, some have begun to question the value of OBCS for patients and in particular which patients should be selected for more complex forms of surgery – namely level II OBCS techniques (therapeutic mammoplasty and chest wall perforator flaps).

This review represents a commendable although arguably over-ambitious attempt to assess the benefits of OBCS in terms of clinical and patient reported outcomes with emphasis on local recurrence, distant and overall survival together with quality of life. The paper also addresses the shortcomings of surgical training of breast surgeons throughout continental Europe. Interestingly there is no reference to the Association of Breast Surgery (UK) that does have a well-organized training program for breast surgeons – there is an excellent portfolio of courses and several oncoplastic fellowships (either confined to the UK or linked with centers in Europe and the United States).

Reply: Page 5, lines 579-582. We added a reference from the Association of Breast Surgery (ABS)

The paper includes a comprehensive list of references but the review is essentially narrative with no formal analysis to support many of the statements that are very superficial and lack any depth of discussion. There is no assessment of the quality of papers that are cited and an important systematic analysis using the GRADE approach conducted by colleagues in Europe is missing [Rocco N, Catanuto G, Cinquini M, Audrestsch W, Benson J, et al. Breast 2021; 57: 25 – 35]. I note the authors have also omitted to mention the large NSABP B-06 trial in the context of breast conserving surgery and refer only to the Milan and EORTC trials.

Reply: Page 22, lines 505-507. We added the mentioned references

A notable aspect of the review is the poor standard of English and imprecise use of language – some phrases and sentences are difficult to understand (‘curing them better’).

Reply: A native English translator has made corrections

Furthermore, when referring to studies comparing OBCS to mastectomy, it is unclear whether this relates to mastectomy alone or with immediate/delayed breast reconstruction. The authors refer to a paradigm shift – but I cannot detect what this is! There is a shift at present towards minimizing OBCS and avoiding interventions that do not improve overall health-related quality of life. The concluding statement in the abstract is very non-specific and rather weak.
What is meant by the ‘change of paradigm’ of breast surgery in 2010 and 2014 – I am not aware of these two dates having particular significance for OBCS – of course 2014 was the year when there was consensus on the definition of a negative margin of resection for breast conserving surgery – which ironically was ‘no ink on tumor’ – hence wider margins of resection that are achievable with OBCS may not be necessary!

- Reply: Page 3, lines 68-78. We have clarified the concept of paradigm shift in the text
- Reply: Page 2, lines 47-51. We revised the concluding statement in the abstract to be more

specific

I agree that studies often fail to include data on the proportion of patients with either volume displacement or replacement techniques; this is especially important for quality of life outcomes as additional morbidity can be incurred from transposition of a chest wall perforator flap.
The discussion on re-excision after OBCS should have mentioned studies of therapeutic mammoplasty by Douglas McMillan showing that the margin positivity rate is about 10% and usually involves multiple margins that necessitate mastectomy rather than re-excision. There is no reference to use of MRI when discussing rates of conversion to mastectomy. What do the authors mean by margin involvement being 'small and focused'. Is this focal involvement? Sometimes we do not excise for a single margin with focal involvement only.

- Reply: Page 10, lines 210-212. We added data about MRI
- Reply: Page 10, line 215. We changed "small and focused" to focal involvement

The paper by Van La Parra (reference 24) referred to extreme oncoplastic surgery for patients with extensive DCIS and not downstaging of large invasive cancers after neoadjuvant chemotherapy.

- Reply: Page 29, line 722. The reference is incorrect; we are referring to another article by Van la Parra: van la Parra RFD, Clough KB, Thygesen HH, Levy E, Poulet B, Sarfati I, Nos C. Oncological Safety of Oncoplastic Level II Mammoplasties After Neoadjuvant Chemotherapy for Large Breast Cancers: A Matched-Cohort Analysis. Ann Surg Oncol. 2021 Oct;28(11):5920-5928. doi: 10.1245/s10434-021-09829-8. Epub 2021 Mar 28. PMID: 33778905.

Patients will agree to delayed symmetrization when this approach is recommended by a surgeon and they have been given fully informed consent. Often the breast on the therapeutic side is made slightly larger (10%) to compensate for loss of volume with radiotherapy.
What is 'mastectomy bed radiation' – do the authors mean post-mastectomy irradiation (chest wall irradiation)?

- Reply: Pagee 12, line 265. Yes, We have changed the term in the text

There should have been a reference to the Dindo classification of complications into minor and major.

- Reply: Page 12, line 269-274. We added Dindo classification in the text

The authors should be careful when attributing complications to 'technical flaws' and implying suboptimal surgery. Sometimes wound breakdown will happen because patients are current smokers, diabetic or have received previous breast irradiation or cosmetic surgery to the breast. The authors should have provided some data on delays in starting adjuvant treatments consequent to complications. Delays in commencement of chemotherapy is a particular concern if the patient is node positive and likely to have micro-metastatic disease.

- Reply: Page 13-14. Lines 301, 307. We added some data about complications and delay treatment

Line 282 – what are the physical sequelae that are lower for OBCS? Is this compared with standard BCS? Chest wall perforator flaps are likely to increase physical side effects of surgery (this is referred to in lines 335 – 337).

- Reply: Compared to mastectomy, not standard BCS. We changed in text.

Line 317 – I think it is important here to mention tumor size and location; for larger primary tumor

in cosmetically sensitive zones of the breast, OBCS will yield significantly improved aesthetic outcomes compared with conventional breast conserving surgery.

- Reply: We added the comment

The section on sexual well-being is interesting and well-written; this does review an area that tends not to be discussed in detail in other reviews. Improved scores for psychosocial and sexual well-being amongst patients undergoing OBCS rather than mastectomy and immediate reconstruction is important (reference 61).

The authors should have mentioned patient expectations in the section on standardization and evaluation of oncoplastic techniques. This is a challenge at the present time and is leading to high rates of litigation relating to breast surgery in many countries.

- Reply: We added the comment

Reference to newer techniques for training surgeons involving simulation and virtual reality is important but ultimately surgery is an apprenticeship and there is no substitute for learning from performance of operations under appropriate supervision. A combination of techniques is important. I am not sure how prescriptive we can be with numbers of cases – training is competency based and it is acknowledged that some trainees need longer to train (more cases) than others.

Lines 156 – 157 – sentence difficult to understand (also ‘margin expansion’ – line 159).

Reply: We change the concept for margin re-excision

The paper focuses on the debate about the role of OBCS and its implementation in routine clinical practice, but these two aspects should have been discussed more critically and comprehensively within the text. Are the authors implying these techniques should become more widely available (especially in smaller non-teaching/University institutions) in general without any concerns about over-application of these techniques in some units by oncoplastic enthusiasts?

Reply: We attempted to introduce pertinent information related to oncoplastic breast-conserving surgery into the literature.

The authors have referred to evidence being ‘uncertain’ or ‘very uncertain’ but have not defined exactly what this means. There is no discussion of GRADE criteria and a more in depth discussion of local recurrence and survival would be appropriate – for example, why do the authors think that patients undergoing mastectomy and reconstruction demonstrate less difference or equivalence of outcomes to OBCS compared with mastectomy patients alone – is this because of selection bias with reconstruction patients having smaller and more favorable tumors (less likely node positive).

Reply: We added the comment in the text