Peer Review File

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Reviewer A

Comment: Thank you for your nicely designed paper on this problem

Response: I would like to express deep appreciation for the kind and meticulous review of our article. We hope that our findings will aid surgeons in becoming aware of these changes after breast implant insertion.

Reviewer B

Comment: Overall, it is a concise and well-written article. However, in the case of capsular contracture, it occurs well when RT is received in the subpectoral plane. So it should be discussed in detail. The conclusion that age is an independent prognostic factor of CWD can also be biased depending on the proportion of capsular contracture in patients with age. If capsular contracture was higher in younger patients, age would be a statistically significant risk factor. Therefore, it should be suggested that there is no difference in the proportion of capsular contracture over the age.

Response: Some studies have reported that the possibility of capsular contracture increases when RT is followed by subpectoral DTI. Moreover, these studies mention that capsular contracture and displacement of underlying implants after PMRT is caused by skeletal muscle fibrosis and contracture. However, there was no significant difference of capsular contracture in our cohort. This seems to result from, as mentioned in the surgical technique, sufficient release of the pectoralis muscle for minimizing complications, including animation deformity.

Intraoperatively, the pectoralis muscle is sufficiently released from its insertion and ADM was widely applied to cover the inferior pole. In our institute, subpectoral DTI was performed only when the mastectomy flap was thin and there was a possibility of related complications such as infection or capsular contracture. We believe that sufficient release of the pectoralis major to prevent animation deformation works as an adequate defense measure against capsular contractures caused by fibrosis of muscle. The number of prepectoral receiving RTs was 16 among 42 and that of subpectoral was 6/15; both groups showed no statistically significant difference in the CC occurrence in the subpectoral group with PMRT. We have added information to further elaborate on these surgical techniques in the Method section (Lines 110–115, 243-247).

Reviewer C

Comment 1: This is a retrospective study of chest wall deformity after implant insertion intended to measure the deformity and to identify risk factors. It is stated as a conclusion of the study that implant reconstruction may cause chest wall deformity, which is an important and well described

consequence in concordance with the literature.
The population of the study is very heterogeneous (different types of reconstruction, size of implants from 125-500cc) with a low number of participants despite its heterogeneity (n=57).
The main limitation of this study is the statistical analysis carried out, since univariate analysis is carried out to identify the main risk factors. It is not understandable to make a multivariate linear regression after doing a univariate analysis, since confusing factors may be involved.
In this multivariate analysis, there are not included very important factors as implant volume and plane of reconstruction, despite not being statistical significant in the univariate analysis (We insist, there could be confusing factors). Further more, there is a low correlation coefficient for determination (r2=0,339) (the average number of r2 should be at least more than 0,5; less than this is a model not well correlated).
If we exclude the multiple regression analysis, the conclusions are poor.
Response 1: We appreciate your advice. To obtain meaningful results on multivariate analysis, univariate analysis was usually performed for the process of selecting significant variables. Although it varies from study to study, multivariate analysis can be performed including variables with a low *p*-value (less than 0.2 or less than 0.3). Due to the nature of multivariate analysis, as the number of variables increases, the R^2 value increases, but this can reduce the reliability of the model. The adjusted R^2 is a modified version of R^2 that has been adjusted for the number of predictors in the model. In this respect, we tried to obtain a model with the highest adjusted R^2, not R^2, and selecting variables through univariate analysis was one of the processes used for this model.
A high R^2 of above 0.60 is required for studies in the pure science field because the behavior of molecules and/or particles can be reasonably predicted to some degree of accuracy in science research; while a low R^2 can be accepted for medical studies because the results of medical treatment cannot be accurately predicted, an R^2 value around 0.3 is also considered valuable depends on research and research variables. Moreover, a low R^2 value means that the model has low predictability, but is not related to the reliability of the variables. We think that the low predictive value comes from the process of converting the categorical variables to dummy variance, so the significance of each variables is still meaningful. The low R^2 value (poor predictiveness of the model) is considered to be a matter of the prediction model and can be improved by further studies with larger numbers of patients. We were also concerned about the low R^2 value, but we think that it is still meaningful as a result of this study. We appreciate your insightful and valuable comment.

Comment 2: Another relevant point is that some of the main variables in the analysis is the capsular contracture. But the main issue is that time of follow-up is poor to identify capsular contracture and also this item has a relevant subjectivity (which is kindly mentioned in the text).

Response 2: As you commented, a relatively short follow-up period may not be a sufficient period to observe capsular contracture, so it can be a major limitation of this study. However, as postoperative chest wall change does not progress like a linear function graph, measuring the AP length of the chest wall at the same time after surgery was very important in the methodology of this study. We hope that you understand the reason for the insufficient follow-up period; we have added this point as a limitation of the study. (Line 261-265)

Minor changes:
Comment 3: Table 1: adyuvant therapies (it is not included the %); Follow-up period (it is not included the unit of measure, it is assumed it is months)
Response 3: Thank you for your valuable comments. We have corrected what you pointed out in Table 1.

Reviewer D
I appreciate for the opportunity to review paper: GS-22-101-R1-RV8-5705, # 89776 Risk factors for chest wall depression after implant insertion for breast reconstruction: a retrospective quantitative study. Here the authors report their experience in oncologic breast reconstruction looking at chest wall deformation following implant insertion. More specifically they quantified chest wall depression (CWD) after breast implant insertion and identified possible risk factors.

First, I would like to congratulate the authors for looking into this interesting topic related to chest wall deformity after DTI (Direct to Implant) breast reconstruction. This is a 3 year retrospective review, well written and applying good reconstructive principles.

Comment 1: However, I have several concerns with the study: There are two groups of patients, sub pectoral and prepectoral, which is like comparing apples and oranges. There are two different techniques which have different surgical approaches. This was not consider within the analysis and all patients were part of the same group.
Response 1: We agree that there is a big difference between subpectoral and prepectoral. However, this is also one variable in statistical analysis. CWD is the dependent variable in this study; the plane of inserted implant is one of many variables and has no other meaning. In that context, it can be said that RT was actually a more important variable, as seen in the results. Since the multivariate analysis was performed to consider the effects between all these variables, we should analyze statistical results considering ‘the implant plane’ as one of many variables.

Comment 2: In addition, the follow-up period is to short, only 1 year? How fast can these patients develop capsular contracture in one year. In addition, more than (60%) of the patients had Grade I capsular contraction. How can the authors explain these findings and that such minor grade can be associated with these findings? Capsular contracture is a very, very subjective measurement.

Response 2: Grade I is considered as no capsular contracture and patients are considered to have capsular contractures from Grade II. Although CC is a subjective test, there was a significant difference between Grades I and II. To minimize the variables in this regard, a single senior surgeon determined the Baker grade. We have added this explanation and limitation in the Discussion section (lines 237-241).

Comment 3: In addition, a good proportion of the patients received adjuvant radiation therapy. This has been published extensively regarding the effects of postoperative radiation. How can the authors prove that what they were describing was not postoperative radiation effects vs real capsular contracture? Was there any difference between Cap I and Cap III with our without radiation?

Response 3: In the case of Grade III, it is possible to distinguish it from changes due to RT, but there is a possibility that Grade II capsular contracture may be confused with soft tissue changes after RT. Therefore, although we have mentioned this point in the Discussion, even if it is CC grade II, experienced breast surgeons can distinguish it in most cases.

We have added this explanation in consideration of the mutual influence of RT and capsular contracture, which may be the results of statistical analysis. However, we think collinearity and correlation should be used differently in statistical analysis. If collinearity is high (>10), two variables should not be analyzed together. However, even if there is a correlation between two variables, it is possible to include them in multivariate analysis if the collinearity is low.

From multivariate analysis, the fact that RT was omitted from the significant factor in multivariate analysis can be considered that CC caused by RT rather than RT itself is a significant factor. We have added this explanation in the Method and Discussion sections. (Line 139, 242-247)

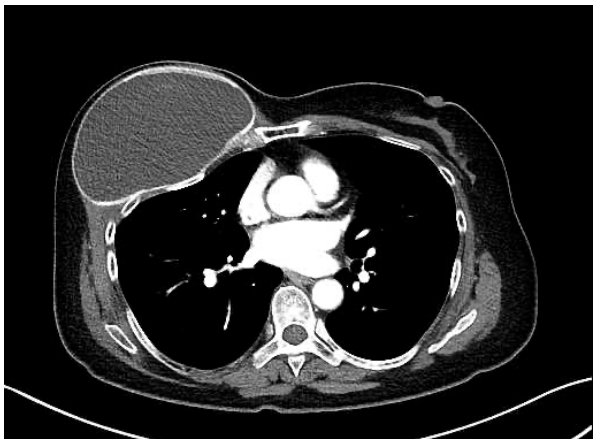
Comment 4: In the discussion the authors mentioned that the breast tissue in younger patients, due to its density could cause the rib side effects? If the breast tissue is removed during the mastectomy how can the explain this comment?

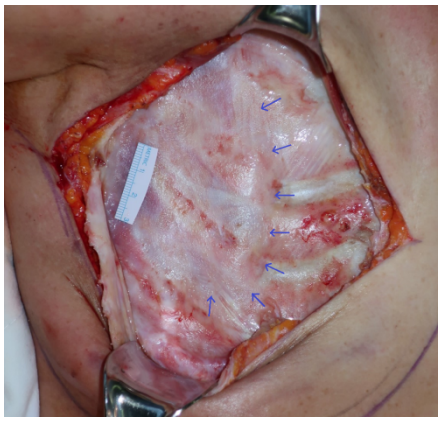
Response 4: I appreciate your insightful and valuable comment. We misdescribed the mention of 'dense breast' in the process of expressing ptotic breasts with loose soft tissue in older patients. We intended that the vector of influence of the implant was not dispersed due to the non-ptotic breast, not that the influence of the implant was increased due to the dense breast. We have

corrected this part, which can be misunderstood. (Line 214-215)

Comment 5: Also the other finding they discuss is patients age. Hard to understand that younger patients had more rib deformities? Overall all, I believe there are a lot of methodology issues and confiding factors that cannot be explained with their findings and just some of these hypothesis does not add anything to the breast reconstruction literature. The group analyses was also not accurate but I understand that due to the low volume of patients, a subgroup analysis can not be performed. For these reasons, I don't think this paper has the minimum requirements to be published.

Response 5: Plastic surgeons often need to take a rib cartilage for ear or nasal reconstruction. Usually, the cartilaginous portion remains until the age of 30-40 years, so the cartilage can be easily harvested with a blade. However, in patients over the age of 50 years, the cartilage part is completely replaced with bone, so it becomes very hard. In addition, it is a well-known phenomenon that cartilage is deformed by continuous pressure. [1] In our experience, in patients with a deformity of 10 mm or more, the depression occurred mainly on the cartilaginous portion. This phenomenon has not been reported before, and it was observed intraoperatively when we changed breast implant in some cases. (Figure attached) Although the attached figure in our case is a tissue expander, not an implant, but we can observe that there is a depression mainly in the cartilaginous portion. References have been added for these parts. (Line 208-210)





Reviewer E

The aim of the study was to quantify chest wall depression after implant-based breast reconstruction using pre- and postoperative CT scans and identify possible risk factors. They concluded that DTI breast reconstruction poses a risk of developing chest wall deformity and that older patients and patients who develop capsular contracture are significantly more likely to have chest wall deformity.

The authors should be complemented on a well-executed study. However, the

clinical relevance, implications and the applicability of the results seem unclear and should be highlighted throughout the manuscript.

Background

Comment 1: - This section needs to concern current knowledge about chest wall deformity and what clinical implications it has for the patients to highlight the relevance of the study. I recommend including findings from previous studies and which new question this study is trying to answer. The listing of all other implant-related complications to breast reconstruction seems irrelevant and should be left out of the background section.

Response 1: Thanks for your comments. There are few studies that can be used as references because we could not find previous studies suggesting that chest wall deformation may occur due to breast implants. Instead, we found some reports that depression comes after tissue expander insertion, so this has been described in the Discussion and partly added to the Introduction. As you commented, we have removed the contents of implant-related complications including breast implant illness.

Methods

Comment 2: - Is it standard treatment for all patients to get a pre- or post-op CT-scan? If not, please clarify why the patients underwent a CT-scan? (line 84-85) Please mention how many patients were identified by the chart review and how many were excluded due to missing CT-scans?

Response 2: In our institute, a preoperative work-up CT is performed one month before surgery, and a follow-up CT is performed one year postoperatively. To control the time variance in analysis, the measurement was performed with these pre- and post-operative CT. (Line 261-265) The reason for the small number of patients is because we considered that we enrolled cases in which a single breast surgeon and a single reconstructive surgeon were paired to reduce the influence of surgical factors, different treatment protocol.

Comment 3: - In this study, patients are excluded if they undergo two-stage breast reconstruction with an expander implant and results are only included for DTI. I think it is relevant to look at patients undergoing two-stage breast reconstruction as well to compare with patients undergoing DTI and compare with previous studies.

Response 3: I appreciate your insightful and valuable comment. We collected data about two-stage reconstruction, but the patient group who underwent 2-stage operation with tissue expander showed a recoiling phenomenon, which is recovery of the chest wall depression after removal of expander removal and implant insertion. Since this is a completely different phenomenon, we tried to write a different article about this this phenomenon. We hope that you understand the reason for excluded data.

Comment 4: I think it is a great idea that the authors use a chest wall deformity index (CDI) to account for the influence of respiration when performing a CT-scan. However, I think the terminology used for the A-P measurements is a bit confusing as both L1/L2 (L1'/L2') is used for the pre- and postoperative scan. I think it would be beneficial for the understanding if the term for the post-operative measurement was different.
Response 4: Thank you for your valuable comments In this regard, we changed L1'/L2' to P1/P2 for better understanding.

Comment 5: - In the study, the chest wall deformity is measured at a single point (maximum A-P distance at costa 4). I believe it would improve the method significantly, if the authors measured multiple A-P distances from different slides of the CT-scan where the implant is visible.
Response 5: At first, we measured 3 points (2nd, 4th, and 6th rib), but the part where depression mainly occurred was concentrated at the central point of the implants, and in particular, almost no depression occurred in the upper part. Therefore, we analyze the depression degree by selecting one point where the most significant depression can be observed. We hope that you understand this methodological issue.

Comment 6: - How was a correct position secured when performing the CT-scan? In our experience, even the smallest rotation on a vertical axis can produce differences in alignment that wrongfully could be described as chest wall deformity. If the patients were placed in a prone position, there is a risk that the chest wall deformity is cause a direct impact of pressure on the implant. If the scans were performed in a supine position, I would recommend the authors to specify this in the manuscript.
Response 6: I appreciate your valuable comment. As shown in Fig. 1, the midline connecting the spine and the sternum was set as the vertical axis and the antero-posterior (AP) length was measured with a straight line parallel to it. In addition, all CT scans were performed with the patient in a supine position. We have added this method of measurement in the Method section (Line 123-125) However, in patients with disorders such as scoliosis, their condition can affect the accurate measurement, and this point was added as a limitation. (Line 267-268)

Statistics:
Comment 7: - The authors report in the result section that they have used a paired t-test. Please report this more clearly in the methods section and clarify when you use an unpaired vs paired t-test.
Response 7: Since we compared before and after surgery in the same patient, paired t-test was used to verify the validity of the difference in length. We have added this comment in the Method section. (Line 133)

Comment 8: - Throughout the manuscript, the authors use ranges a measure of variance. I recommend using confidence intervals, SD or IQR to report on the variance of your estimates as this is significantly more informative for the readers.

Response 8: Thanks for your comment. We have added standard deviation of Age, BMI, and Follow-up period to Table 1.

Comment 9: - The authors use multiple t-tests to determine correlation between continuous variables and CDI and afterwards significant variables are included in a multiple linear regression. I recommend that the authors include all variables (risk factors for CWD) in one multiple linear regression model (table 3 and 4 of both categorical and continuous outcomes). If this provides unstable estimates, please perform stepwise univariate linear regression to determine which variables precede to the multivariate linear regression.

Response 9: Thank you for your kind advice. We tried to obtain a model with the highest adjusted R^2, not R^2, and selecting variables through univariate analysis was also a process used for this model. Due to the nature of multivariate analysis, as the number of variables increases, the R^2 value increases, but this can reduce the reliability of the model. When we performed the analysis with all variables, the R^2 values were higher, but the adjusted R^2 values were lower. We hope that you take these points into consideration for not performing statistical analysis with all variables.

Results:

Comment 10: - The authors report the when the post-operative CT scan was conducted. It would be informative to also include when the pre-operative CT scan was conducted.

Response 10: In our institute, a preoperative work-up CT is performed one month before surgery, and a follow-up CT is performed one year postoperatively. We have added this information (Line 262-265)

Comment 11: - Which patients where considered to have capsular contracture? It seems as though the authors included Baker II, which normally is not considered a degree of capsular contracture on the Baker scale from I-IV. I recommend only including patients graded as Baker III.

Response 11: Even if there was no significant abnormality in appearance, if hardness is present around the implant on physical examination, it was classified as Baker II. This was recorded as distinct from Baker I, which is the completely normal state. Because the Baker grading system is a subjective test, Grade II may be interpreted close to normal, but in this study, II was included when there was a distinct difference in palpation. We have added more comments about this Baker grading in the Method section. (Line 95-98) It is thought that the relatively short follow-up period also had an effect on the low rate of Grade III or IV, and

the one-year follow-up period is one of the limitations of this study as mentioned by the reviewer above.

Discussion:

Comment 12: - Please start the discussion section of the manuscript by mentioning the key results of your study.

Response 12: Thank you for the valid point. We have added the mention of key results in the Discussion section (line 172-176).

Comment 13: - The authors find that an independent risk factor for CWD is age and hypothesize that it could be due to the fact that younger women have relatively smaller and denser breast which can increase the pressure induced by the implant. It would be beneficial to use the pre- and postoperative scans to perform an analysis of breast volume to test this hypothesis.

o Ref: Herly, M., Ørholt, M., Müller, F. C., Hemmingsen, M. N., Hansen, J., Larsen, A., ... & Vester-Glowinski, P. V. (2020). New Validated Method for Measuring Fat Graft Retention in the Breast with MRI. Plastic and Reconstructive Surgery Global Open, 8(8)

o Ref: Herly, M., Müller, F. C., Ørholt, M., Hansen, J., Sværke, S., Hemmingsen, M. N., ... & Vester-Glowinski, P. V. (2019). The current gold standard breast volumetry technique seems to overestimate fat graft volume retention in the breast: a validation study. Journal of Plastic, Reconstructive & Aesthetic Surgery, 72(8), 1278-1284.

Response 13: I appreciate your insightful and valuable comment. As we answered to Reviewer D, we misdescribed the mention of 'dense breast' in the process of expressing ptotic breasts with loose soft tissue in older patients. We intended that the vector of influence of the implant was not dispersed due to the non-ptotic breast, not that the influence of the implant was increased due to the dense breast. We have corrected this part, which can be misunderstood. (Line 214-215)

Comment 14: - I recommend that the authors elaborate on the limitations of their study. E.g. it would be beneficial to elaborate on the uncertainty of the positioning of the patients during the CT scans in the limitation section of the discussion.

Response 14: I appreciate your valuable comment. As shown in Fig. 1, the midline connecting the spine and the sternum was set as vertical axis and antero-posterior (AP) length was measured with a straight line parallel to it. In addition, all CT scans were performed with the patient in a supine position. We have added this method of measurement in Method section (Line 123-125) In patients with scoliosis, the condition can affect the accurate measurement, and this point was added as a limitation. (Line 267-268)