Peer Review File

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**Reviewer A**

This is an interesting manuscript on IBR or DBR. I think this manuscript can be accepted for publication.

**Reviewer B**

The paper "Comparison of one-stage direct-to-implant with acellular dermal matrix and two-stage immediate implant-based breast reconstruction. A cohort study" by Mette Eline Brunbjerg et al. presents an observational cohort study that compares direct to implant with ADM versus two stage expander-to-implant breast reconstruction. The paper is well written and the issue studied is interesting, though has already been studied extensively. I have major points of criticism and comments for the author

Comment 1:

Several parameters may bias the results of the study, some of them due to the methodology of the study:

Comment 1a:

On what basis was the decision made to perform the two stage surgeries- due to a concern about the viability of the mastectomy flaps?

Reply 1a:

The decision to perform immediate two-stage breast reconstruction in the two-stage treatment group was made only based on inclusion time before December 2012 as this was our standard care option at that time. One patient (one breast reconstruction) in the one-stage group underwent two-stage expander-based breast reconstruction due to vulnerable mastectomy flaps as described in Figure 1.

Changes in the text:

None

Comment 1b:

Couldn't find patients who underwent prior lumpectomy and radiotherapy, were they excluded from the study?

Reply 1b:

No patients undergoing prior lumpectomy or radiotherapy were excluded, but unfortunately this was not reported in the manuscript.

Three patients in the two-stage group underwent prior lumpectomy and two patients in the one-stage group underwent prior lumpectomy. None of these patients experienced minor or major complications after breast reconstruction. Patients that were expected to undergo radiotherapy following immediate breast reconstruction were, at the time of the study, not offered any kind of implant-based breast reconstruction.

Furthermore, a typing error was discovered in table 1 in the section "Indication for mastectomy" where the numbers given in the one-stage group was unfortunately not correct.

Changes in the text:

The following sentence is added in line 294: Three patients (three breasts) in the two-stage group and two patients (two breasts) in the one-stage group underwent prior lumpectomy.

Table 1 "Indication for mastectomy" where one-stage group/DCIS is changed from 5 to 4 and one-stage group/Prophylactic is changed from 14 to 13

Comment 1c:

Different general surgeons, 4, and plastic surgeons, 3, performed the surgeries in different time period, experience bias?

Reply 1c:

The same team of surgeons (general and plastic surgeons) were performing the surgery during the entire study period in both treatment groups. These surgeons were already experienced from the beginning of the study and no experience bias is anticipated in the two-stage group. Though, as described in the text line 437 this might be a factor for the plastic surgeons in the one-stage group.

Changes in the text:
The following was added to the sentence in line 441: “during the entire study period”.

Comment 1d:
Size of the implant in the two-stage group was 100 ml larger than in the one stage, could increase the complications in this group.
Reply 1d:
Yes, this is a possibly explanation for the complication rate in the two-stage group.

Changes in the text:
The following sentence was added in line 385: “Furthermore, the final implant size in the two-stage group were in average 100 ml larger than in the one-stage group and this might also contribute to the high rate of implant loss and complications in this treatment group”.

Comment 1e:
Difference in antibiotics regimen, could bias the results in consideration with the high rate of cellulitis in the two-stage group.

Reply 1e:
Yes, the difference in antibiotics regimen could potentially affect the risk of infectious complications in the two-stage group.

Changes in the text:
The following sentence is added in line 375: “Furthermore, the two-stage group did not receive prophylactic antibiotic treatment for three days postoperatively as the one- stage group did. This could potentially affect the risk of infectious complications.”

Comment 2:

The study groups are limited, 15 patients in one stage group and 19 in two stage group completed follow-up period of 2 years, much smaller than previous studies, including the study by Dikmans RE et al.

Reply 2:

Yes. We agree that the study size is limited and therefore, we acknowledge the limitations for drawing wide conclusions as mentioned in the conclusion line 466 and in study limitations line 434.

Changes in the text:

None

Comment 3:

The majority of the implant losses in the two-stage group, 4/5, occurred at the exchange surgery, a very high percentage, much higher than published during this stage, supposed to be the safer one.

Reply 3:

Yes. A higher percentage of implant loss were observed in the two-stage group than expected. We propose, that the reason is a larger average implant size in the two-stage group resulting in an internal pressure of the skin leading to a higher risk of complications resulting in implant loss.

Changes in the text:

The following sentence is added in line 385: “Furthermore, the final implant size in the two-stage group were in average 100 ml larger than in the one-stage group and this might also contribute to the high rate of implant loss and complications in this treatment group.”

Comment 4:

The questionnaire used during the study is not a validated one.

Reply 4:

At the time of study start unfortunately no danish validated version of e.g. Breast-Q was available as stated in line 230. But the study specific questionnaire used was previously used in our department and the internal consistency of the aesthetic satisfaction scale was found excellent (Cronbach’s alpha=0.96).

Changes in the text:

The following sentence is added in line 232: “The internal consistency of the aesthetic satisfaction scale was found excellent (Cronbach’s alpha=0.96).”

**Reviewer C**

This study is about the comparison between DTI (direct to implant) with ADM (acellular dermal matrix) sling and two-stage BR (breast reconstruction) without ADM.

Comment 1:

Introduction

It is necessary to comment the previous researches on the comparison between one-staged (DTI) IBR and two-staged IBR in terms of indications and outcomes.

Reply 1:

References has been added regarding the proposed advantages of ADM assisted one-stage breast reconstruction and regarding the aesthetic outcome in comparison of the two techniques.

Changes in the text:

The following was added to the sentence in line 132: “whereas the overall advantage with the one-stage approach is the reduced need for outpatient visits for expander fillings and the possibility to avoid a second operation in general anesthesia for exchange of the expander to silicone implant. The literature suggest that the one-stage approach entails a higher risk of complications as infection, necrosis and implant loss compared to the two-stage approach (5-7).”

The following sentences was added in line 146: “The aesthetic result has been reported higher when breast reconstruction was performed with the use of ADM (10,11) but in a randomized controlled trial (RCT) comparing ADM assisted one- stage BR with submuscular two-stage expander-to implant BR no significant difference between the two groups regarding satisfaction with the breast or the overall outcome was observed (12).”

Comment 2:

Recruitment

171-174 All patients underwent implant-based breast reconstruction (IBR) following skin sparing mastectomy were recruited. Meaning of the skin sparing mastectomy should be clarified whether it means a nipple sparing mastectomy or a skin sparing mastectomy with NAC sacrifice.
In general, when sufficient skin amount with good vascularity is left over after mastectomy, DTIs are usually selected, but if not, two-staged BRs are chosen. Please, add the selection criteria of DTI group and two-staged BR group included in this study.

Reply 2:
The above-mentioned recommendations have been elaborated in the manuscript.

Changes in the text:
The following amendment to sentence was added in line 159: “or nipple-sparing”. The following sentence was added in line 165: “Allocation to either one-stage BR or two-stage BR were based on enrolment time. Patients undergoing BR before December 2012 were assigned to two-stage BR and patients undergoing BR after December 2012 were assigned to one-stage BR.”
The following sentence was added in line 295: “Only one patient in the one-stage group (bilateral BR) underwent nipple-sparing mastectomy.”

Comment 3:
Description of breast implant type is missing. Because of the issue about BIA-ALCL, selection of breast implant is limited to a smooth round implant and the shape of breast implant may considerably influence the aesthetic outcomes of IBR.

Reply 3:
The above-mentioned recommendations have been elaborated in the manuscript.

Changes in the text:
The following sentence was added in line 189: “The expanders used were Natrelle® with self-sealing dome port and the anatomical textured silicone gel-filled implants used were Eurosilicone® or Natrelle®).”

Comment 4:
As aesthetic outcomes, the authors assessed symmetry and capsular contracture. In this

study, bilateral cases are 52%(11/21) in one-stage group and 26%(6/23) in two- stage group. Symmetry can be achieved easily in bilateral cases. Therefore, we can expect the better aesthetic outcomes about symmetry in one-staged group. It might bring a selection bias.

Reply 4:

Yes, there is a potential selection bias in the assessment of degree of symmetry between the one-stage group and the two-stage group. The number of patients with less than 0.5 cm difference in suprasternal notch-to-nipple distance and nipple-to- inframammary fold distance were a bit less (but not statistically significant) in the two-stage group compared to the one-stage group as described in line 340-346. The assessment of symmetry regarding breast size and shape were in both treatment
groups rated very high within the range, without any statistically significant difference between groups.

Changes in the text:

None.

Comment 5:

Generally, description about study seems to be tedious and more concise and accurate explanation about surgical procedures and analysis of outcomes is necessary.

Reply 5:

In general, we find that it is important to provide the readers with an elaborate description of surgical techniques and method of analysis as it is important for interpreting the study results.

Nevertheless, the section “surgical techniques” and “statistical analysis” has been rewritten to a shorter version.

Changes in the text:

“Surgical techniques” text was changed to the following (line 189): “In all cases the implant or expander was placed behind the pectoralis muscle. The expanders used were Natrelle® with self-sealing dome port. The anatomical textured silicone gel- filled implants used were Eurosilicone® or Natrelle®.

Surgical technique for one-stage immediate BR using porcine acellular dermal matrix (ADM) (Strattice™, LifeCell Corporation, Branchburg, NJ, USA) and fixed size silicone

implant:

The pectoralis major muscle was elevated and divided inferomedially. A sizer was used to determine implant size considering the viability of mastectomy skin flaps, assessed clinically. ADM was sutured to the inframammary fold at the chest wall, the fixed sized anatomical implant was inserted and the ADM was sutured to the pectoralis major muscle. Two suction drains were placed, draining the submuscular and subcutaneous pockets.

The surgical technique for two-stage immediate breast reconstruction using temporary expander implant and later exchange to fixed size silicone implant was as follows: A submuscular pocket was created by elevating the pectoralis major muscle, the serratus anterior muscle or its fascia and the anterior rectus sheath. A sizer was used to estimate the expansion volume and the expander was placed. Suction drains were placed, draining the submuscular and subcutaneous pockets. The first expansion was performed two weeks postoperatively and after that at weekly intervals, should no complications arise. Three to six months after the final expansion volume had been achieved the expander was changed to a fixed sized implant. The submuscular pocket was opened, the expander removed and the necessary adjustments of the pocket were performed. A sizer was used to determine implant size and the final size silicone implant was placed. One suction drain was used when deemed necessary. All patients received one prophylactic dose of antibiotic (Cefuroxim or Dicloxacillin) preoperatively and the one-stage group continued Cefuroxim for three days postoperatively. Drains were removed when output was less than 20 ml for two consecutive days."

Statistical analysis" text was changed to the following (line 270):

Descriptive statistics were applied for patients' demographics giving mean and standard deviation for continuous variables. Categorical variables were compared between study arms using Fisher's exact test while continuous variables were compared by a t-test. For the continuous outcome the arms were compared using t-test for two means or were analyzed using a simple linear regression model. A multiple linear regression was used to adjust for BMI etc. Mixed regression model was used wherever it was necessary to adjust for the repeated measurements at the patient level (observations at the breast level), in which case Kenward-Roger approximation as used to adjust for the degrees of freedom due to small sample size. The dichotomous outcome was analyzed using a generalized linear model with identity-link function and in case of repeated measurements, the IDs were used as clusters. The outcome "number of aesthetic

corrections" were analyzed using a Poisson regression model.
Based on clinical experience it was decided to adjust for BMI and smoking in the analysis of postoperative complications. Some of the patients were dropped out after explantation (missing not randomly) and one patient was not willing to continue in the study (missing randomly). For the simplicity, all were treated missing by random and particular instances with missing values were omitted from analysis. The details of the missingness is mentioned in the results section and in table 1, 4 and 5. The significance level was set to 0.05. Statistical analyses were performed using
STATA® software IC16 (Stata Corporation, College Station, TX)."

Comment 6:
Furthermore, it is better to compare the pros and cons of each surgical method with the result of breast Q in each group.

Reply 6:
We agree. At the time of study start unfortunately no danish validated version of e.g. Breast-Q was available as stated in line 231 and 437.

Changes in the text:
The following sentence is added in line 443: "Furthermore, no validated questionnaire as e.g. Breast-Q was used for measuring satisfaction with the result as this questionnaire was not available in a validated danish version at the time of study start."