

## Peer Review File

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Reviewer A

COMMENT #1: I would like to thank and congratulate the authors for their great work and the large case series.

RESPONSE #1: Thank you for your comment.

COMMENT #2: The topic is quite interesting for the readers of the journal. However, the structure of the paper is mainly an observational study/ retrospective case series, with a review of literature in the discussion.

RESPONSE #2: Thank you for your comment.

COMMENT #3: In methods, the authors presented it as a review of literature primarily and then case series. The case series shows an excellent volume of work and extensive database, which are invaluable for such research. The research question was not quite clear though. The review of literature is quite invaluable. The paper could be split into two papers, but after major revisions of the structure. Perhaps a systematic review & case series, but with a clear aim of the research.

RESPONSE #3: Thank you for your comment. The structure of the paper was decided with the corresponding Editor and Journal. We added a hypothesis.

COMMENT #4: In the case series:

113-115: What is the benefit and what were the outcomes of re-attaching the tendon to pec major? Was this compared to those who didn't have this procedure performed?

150 The median preoperative hematocrit was 41% (IQR, 39-43%), what's the significance? Is that the pre or post op? It should be made clearer in the text too.

RESPONSE #4: Thank you for your comment. We added the "preoperative" word to the table and the manuscript. After checking the patients' charts, we did not find a single patient in which re-attaching the tendon to pec major occurred. It was stated in the method section, as this were some remarks the senior authors made for the manuscript. We deleted this segment.

COMMENT #5: Was there significant difference in complication rates amongst the different BMI groups or smokers vs non-smokers?

RESPONSE #5: Thank you for your comment. We added the following segment: We evaluated the effect of obesity and active smoking on postoperative complications. Of all complications, obesity ( $\geq 30$  kg/m<sup>2</sup>) was associated with a higher risk of mastectomy flap necrosis on univariable analysis (18.2% versus 6.2%; OR 3.385, 95%CI 1.332 – 8.606,  $P = 0.0104$ ). After adjusting for hypertension, type of mastectomy (skin sparing versus nipple sparing), laterality of reconstruction (unilateral and bilateral), timing of reconstruction (immediate versus delayed), and immediate fat transfer, obesity was no longer a risk factor for mastectomy flap necrosis (OR 2.258, 95%CI 0.791 – 6.445,  $P = 0.128$ ). We did not find any association between active/current smoking and the risk of

any specific complication.

COMMENT #6: What were the differences between preserving the dividing the nerve?

RESPONSE #6: Thank you for your comment. Nerve transection was performed in 4 reconstructions from 234. These cases were performed by a single surgeon. The sample size was not enough to perform any analysis evaluating the differences between preserving the dividing the nerve.

COMMENT #7: The lipomodelling; was that all in LD or including lipo of pec major as well? What were the factors that helped decision making for LDF + implant versus LDIF (pure autologous reconstruction?

RESPONSE #7: Thank you for your comment. We added the following segment: Fat grafting at the time of reconstruction was also injected into the pectoralis major muscle in 89.2% of the cases and the median volume was 60 ml (IQR, 50-84.5 ml) (Table 3). We also added the following segment which indicates the indication for LDF + implant: In patients with previous history of radiation, lack of soft tissue coverage for immediate prosthesis placement, lack of adequate dorsal subcutaneous tissue to achieve optimal breast volume after reconstruction, and patients with a high risk of ischemic complications desiring implant-based reconstruction, implant-enhanced LDF reconstruction was used.

COMMENT #8: Thanks again for this work. With some restructuring of the paper, it could provide interesting data to the reader of the readers.

RESPONSE #8: Thank you for your comment.

Reviewer B

COMMENT #1: Dear Author, the paper is well-written. The number of cases in the case series is sizable. It seems that you have a high frequency of patients with comorbidities in this series and this may explain the rather high frequency of e.g. wound-dehiscence.

RESPONSE #1: Thank you for your comment.

COMMENT #2: In the discussion you do not discuss you own findings, overall results and complications, and you do not discuss these to the findings of literature. Please discuss the key findings of your case series and discuss these to the findings in literature. The most important first etc. You primarily discuss/compare the findings of the LD to the abdominal flaps, the pedicled TRAM and the DIEP, although this may be interesting to the american audience do to tradition and reimbursement, the international reader would probably also be interested in a comparison to the use of the propeller TDAP/pedicled TDAP as a valid alternative to the LD flap.

RESPONSE #2: Thank you for your comment. We believe the reviewer has a valid point. We decided to add the following segment as it is relevant to breast reconstruction after TOTAL mastectomy:

“Previous studies have demonstrated an association between the standard LDF for

breast reconstruction and important postoperative complications, like back seroma (up to 80%), infection, hematoma, infections, or delay in wound healing.(5,34–36) In this setting, previous studies have shown that the muscle-sparing LDF can reduce the axillary bulk after flap inset, generate less contour deformity of the back, and a significantly reduce donor site morbidity.(34,37) Fauconnier et al. performed a study comparing postoperative complications following standard LDF versus muscle-sparing LDF for breast reconstruction.(34) The authors reported that the duration of surgery ( $135 \pm 72$  min versus  $173.7 \pm 47.8$  min,  $p < 0.001$ ) and length of stay ( $3.8 \pm 1.6$ ) versus  $4.1 \pm 1.6$ ),  $p < 0.001$ ) were reduced using a muscle-sparing LDF for breast reconstruction compared to the standard LDF. Furthermore, the rate of complications regarding formation was significantly lower using the muscle-sparing LDF versus standard LDF (3% versus 55.6%,  $p < 0.001$ ). The thoracodorsal artery perforator (TDAP) flap or propeller TDAP flap have been used in a similar fashion achieving smaller volumes after breast reconstruction.(38)”

COMMENT #3: Furthermore, please explain in the discussion, what novelty of your study/data brings to the reader or if there is no novelty, please explain to the reader, why your results are an important addendum to what we already know.

RESPONSE #3: Thank you for your comment. We highlighted the number of patients included, granularity of data, and type of format used for this manuscript.

Reviewer C

COMMENT #1: This is a review of the literature as well as report on a case series regarding latissimus dorsi flap reconstruction following mastectomy. The authors provide information on the techniques and surgical outcomes of their procedures.

RESPONSE #1: Thank you for your comment.

COMMENT #2: There are some areas of concern in the report and perhaps the authors can comment.

RESPONSE #2: Thank you for your comment.

COMMENT #3: Of those who underwent reconstruction, a total of 61.5% had Stage 0,1 & 2 disease. What were the specific indications for mastectomy as opposed to breast conservation treatment? (BCT)

RESPONSE #3: Thank you for your comment.

Before mastectomy, patients receive preoperative evaluation with surgical oncology and plastic surgery (if the patient desires reconstruction). The decision to undergo total mastectomy versus BCT is taken in a multidisciplinary fashion between the patient and these two specialties.

Of the total subjects evaluated in this series, 47 reconstructions (20.1%) had previous BCT and decided to undergo total mastectomy or complete the resection of the whole

breast due to positive margins, symmetry, and poor aesthetic outcomes. We added the following segment which shows the indications for LDF reconstruction: “The indication for LDF in the setting of breast reconstruction has been reported in previous articles from our institution.(6)”.

Of the 144 patients: 43 Delayed were delayed reconstruction, 23 had total Pre-mastectomy radiotherapy, 40 had Postmastectomy radiotherapy (21 After reconstruction and 19 before reconstruction), 85 had obese, 67 had hypertension, 49 had hyperlipidemia, 23 had diabetes, 67 had formal or current smokers, 31 had adjuvant chemotherapy, and 46 had adjuvant radiotherapy.

As it is evident from this sub-group, patients have several risk factors for complications which make the LDF a safe and reliable alternative for breast reconstruction.

COMMENT #4: It has been reported that BCT results in improved survival outcomes as early as the year 2007 (Martin MA, Meyricke R, O’Neill T, Roberts S. Breast-conserving surgery versus mastectomy for survival from breast cancer: the Western Australian Experience. *Ann Surg Oncol* 2007;14: 157-164), so it would be expected that women would have been appropriately counselled. (Fisher S, Gao H, Yasui Y et al. Survival in stage I-III breast cancer patients by surgical treatment in a publicly funded health care system *Ann Oncol* 2015;1161-1169) It is therefore surprising that with improved survival with BCT, women with stage 0,1 & 2 breast cancer would elect to undergo mastectomy with reconstruction, which is associated with significant morbidity.

RESPONSE #4: Thank you for your comment. The author is right. Some of them have had partial mastectomy (BCT) and radiotherapy, and underwent complete mastectomy and reconstruction to optimize aesthetic outcomes (at least 12%). Furthermore, patients are extensively counseled on their options, including BCT and radiation, and several of these prefer total mastectomy plus flap, implant, or implant+flap. We currently do not know what percentage from our whole breast cancer population select to undergo BCT versus total mastectomy.

COMMENT #5: With respect to morbidity, the authors reported in Table 5, recipient complications of 64.6% and donor site complications of 25.7%. revision procedures were performed for 43.6% of the patients. These data appear to be high. Could the authors please provide comparative data from their literature review?

RESPONSE #5: Thank you for your comment. We added the following segments as suggested by the reviewers:

In comparison to previous studies, high rates of complications were evident in our analysis for both the recipient- and donor-site.(21) For instance, twenty three patients underwent immediate breast reconstruction with LIFT in a series reported by Santanelli di Pompeo exhibiting no complications.(21) The mean age was 52.3 years, similar to our series, but the BMI was significantly lower when compared the one of our patients (24.77 kg/m<sup>2</sup>). Data regarding comorbidities and adjuvant chemotherapy and radiotherapy were not reported. In another contemporary study evaluating outcomes of

LDF without implants, the rates of hematoma (4.7%) and seroma (4.7%) were comparable to our results (hematoma, 3%; seroma, 7.7%).(22) In the same study, Leuzzi et al. reported a rate of SSI of 2.4%, which is significant lower to the SSI rate presented in this study.(22) Remarkably, from our series, only 3.8% of the breast required any intervention to manage SSI. Further analysis evaluating the series of Leuzzi and collaborators also demonstrated that most of the reconstructions were delayed (95.2%) in comparison to our study, in which most procedures were immediate reconstructions (69.7 %). This may also explain the high rate of wound disruption events found after LDF reconstruction found in our series, as this complication pertains more to the vascularization of the native mastectomy flaps, rather than the LDF itself.(23,24)

Regarding the rate of postoperative revisions, several retrospective series have reported a revision rate of up to 50% following LDF reconstructions.(24–27) In our study, the rate of postoperative revision to address soft tissue excess was 40.6%. Previous studies have demonstrated a higher rate of additional surgeries compared to abdominal-based free flaps following unilateral, delayed breast reconstruction after PMRT (92.1% vs 67.3%;  $P < 0.001$ ). (28) Other series comparing the rate of revision procedures between LIFT and abdominal free tissue transfer have demonstrated comparable outcomes between groups.(29)

COMMENT #6: Is there a minor phrasing issue in line 321? The beginning of the line should read 'On the other hand' rather than 'On another hand'?

RESPONSE #6: Thank you for your comment. It was corrected.

Reviewer D:

COMMENT #1: Accept

RESPONSE #1: Thank you for your comment.

Reviewer E

The presented information does not provide a lot of new information, however a review which combines all available information can certainly be beneficial. The manuscript is nicely written, see the attachment for my feedback.

Methods

COMMETN #1: Between methods and the following text a sub head named review needs to be inserted.

RESPONSE #1: Thank you for your comment. We followed the reviewer's suggestions.

COMMETN #2: Why did the authors choose to only search Web of Science and PubMed instead of other databases such as Embase?

RESPONSE #2: Thank you for your comment. Literature on breast reconstruction with the latissimus dorsi flap is extremely extensive. We believed that the literature from two databases was enough. As suggested by the reviewer, we also checked EMBASE and SCOPUS. Most articles in these databases were also found in PubMed and Web of

Science.

COMMETN #3: In line 95, the authors stated the included articles reporting on..... I wonder how many articles are included.

RESPONSE #3: Thank you for your comment. We added the number to the chart.

COMMETN #4: This leads to the third question: Can you provide a flowchart to give an overview about how you selected the articles → How many articles did you originally found, how many were excluded (and based on what) etc.

RESPONSE #4: Thank you for your comment. The methodology that was implemented was a narrative review and case series as requested by the journal. We believe the author is requesting a PRISMA Flow Chart. We added a flow chart as requested.

COMMETN #5: Please insert a table which provide an overview of the included studies in this review.

RESPONSE #5: Thank you for your comment. We added the table as supplemental data.

COMMETN #6: Perhaps it is only required in a systematic review, but to enlarge the readability of the manuscript it would be nice to have a detailed research query.

RESPONSE #6: Thank you for your comment. We mentioned the search terms in the methodology. These were as follows: “latissimus dorsi”, “breast”, “cancer”, “reconstruction” and “flap”.

COMMETN #7: Is this review registered on Prospero (or something similar)? If not please do so.

RESPONSE #7: Thank you for your comment. The International Prospective Register of Systematic Reviews (PROSPERO) is an open access online database of systematic review protocols on a wide range of topic. There is no current register for narrative reviews and case series article.

COMMETN #8: How were disagreements between the three reviewers solved? Was another reviewer contacted?

RESPONSE #8: Thank you for your comment. As the following article is not a systematic review, disagreements were not encountered as there was not a formal screening process.

Case series

COMMETN #9: In line 106 there I written that the institutional review board approved this research. Is there a registration number?

RESPONSE #9: Thank you for your comment. We added the following segment was incorporated at the end of the article as requested by the journal editorial office: “*Ethical Statement*: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with

the Declaration of Helsinki (as revised in 2013). The study was approved by institutional/regional/national ethics/committee/ethics board of The University of Rochester Medical Center (NO.: STUDY00007330) and informed consent was obtained from all individual participants.”

COMMETN #10: Line 108 is a bit strange. In this manuscript the surgical technique is not previously reported.

RESPONSE #10: Thank you for your comment. We specified that it was reported in other articles.

Results (demographic and oncologic data)

COMMETN #11: In section data extraction is written that also data about smoking was extracted However, in the results nothing had been described about the incidence of (history) of smoking in the patient population. Can these be added?

RESPONSE #11: Thank you for your comment. Of course, the data is already reported. “Demographic and Oncologic Data” section as follows: The proportion of reconstructions performed in current and former smokers was 6.8% and 36.3%, respectively.

COMMETN #12: Line 182 and 183 are confusing. First I thought patients were discharged from the hospital with a median of three days. But, the median time for removal of the drain was 13 days? How is this possible? Did the authors mean with length of stay, the duration of IC-stay? Please explain.

RESPONSE #12: Thank you for your comment. The median length of stay is 3 days, you are right. Meaning that patients stayed in the hospital 3 days after surgery. The median time for drains removal is 13 days. These (the drains) stay indwelled in the recipient site and donor site, even after hospital discharge, until drainage is less than 30 cc per day.

Reviewer F

COMMETN #1: This article summarizes the issues in breast reconstruction with Latissimus Dorsi Flap, i.e., whether the shoulder and upper extremity dysfunction remain, how nerve preservation contributes to tissue volume maintenance, and the aesthetic results of the donor site and the reconstructed breast. The review section is well organized, but the Case series section needs to be discussed.

RESPONSE #1: Thank you for your comment.

COMMETN #2: It would be better to compare the data with DIEP and TRAM data or at least mention them in the discussion.

RESPONSE #2: Thank you for your comment. We followed the reviewers suggestion as follows: “In a contemporary study, Demiri et al. compared the surgical outcomes of free DIEP flap and extended fat-augmented LDF for breast reconstruction. Patients who received fat-augmented LDF for breast reconstruction were younger ( $p < .001$ ) and had

a lower body mass index ( $p = 0.004$ ).<sup>(15)</sup> While a lower rate of flap-related complications was evident using the fat-augmented LDF (11.1% versus 24.2%,  $p = 0.003$ ), a lower rate of donor-site complications was evident with free DIEP flap reconstructions (20.2% versus 36.1%,  $p = 0.001$ ).<sup>(15)</sup> Remarkably, the donor-site complications found reported with LDF were less severe (e.g., seroma, wound dehiscence, and dog ear) compared to the ones reported using free tissue transfer (e.g., abdominal flap ischemia, abdominal wall bulging, or hematoma).<sup>(15)</sup> Patient-reported outcomes of both groups exhibited similar results between groups for image and shape of the reconstruction, breast symmetry, donor site aesthetic, and overall satisfaction. The aforementioned study suggests that using LDF flap provides comparable outcomes to the DIEP flap for breast reconstruction in terms of patient satisfaction and post-operative complications.<sup>(15)</sup>”

COMMENT #3: Also, the criteria for selecting a Latissimus Dorsi Flap at the institution need to be mentioned. We have described the indications and selection criteria for LDF in previous studies. We added the reference.

RESPONSE #3: Thank you for your comment.