

Peer Review File

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Reviewer A

Thank you for the opportunity to review paper Demystifying Vascularized Lymph Node Transfers and Lymphatico-Venous Anastomoses ATM-23-132-RV8-4524.

Very well written and well summarized. I think it covers from the basics of diagnosis, pathophysiology, classification, radiological assessment, functional and excision procedures as well as a combination of both. In addition, covers all related to physiological procedures. However, I have concerns related to the prophylactic procedures.

Comment 1: Please read recent article by Adam S. Levy and Christine H Rohde et al.... Here, this article was published in the plastic and reconstructive surgery journal where the results of prophylactic surgery are not good at all: Lymphatic Microsurgical Preventive Healing Approach for the primary prevention of lymphoma: A 4-year follow-up. PRS 2022

Reply 1: Thank you for highlighting this important study. We agree that the long-term efficacy of LYMPHA remains poorly understood. Levy et al shed some light on the 4-year outcomes of LYMPHA. In their retrospective review, they conclude that LYMPHA may not prevent lymphedema development in patients undergoing axillary lymph node dissection. However, they acknowledge a number of limitations related to the retrospective nature of their study and small sample size (45 patients). They also acknowledge the need for further long-term studies. This is contrasted by the findings from Herremans et al in their 5-year retrospective review of 132 patients. In this study the diagnosis of lymphedema was made by certified lymphedema therapists in contrast to other LYMPHA studies. They conclude that patients who underwent LYMPHA at the time of axillary lymph node dissection were significantly less likely to develop lymphedema. Another study included a total of 380 patients with a median follow up time of 15 months concluded that the LYMPHA cohort had a significantly lower rate of lymphedema both in univariate and multivariate analysis.

Changes in the text: Page 19, Lines 665-679

Comment 2: When related to the harvest of the VLNT, there are important topics not mentioned within this review. Please include reference: Gastroepiploic Lymph Node Flap Harvest for Patients with Lymphedema: Minimally Invasive Versus Open Approach. Manrique OJ, Chen HC. Ann Plast Surg. 2020

Reply 2: Thank you for highlighting this study. It will certainly further enrich the manuscript and its findings have been added accordingly.

Changes in the text: Page 15, Lines 484-488

Comment 3: When related to the imaging, there is another good summary using these techniques. Please include: Lymphatic mapping and lymphedema surgery in the breast cancer patient. Patel KM, Henderson R. Gland Surg. 2015

Reply 3: Thank you for suggesting this reference. The imaging section in this suggested study was helpful in further expanding our diagnostic modalities section.

Changes in the text: Page 10, Lines 295-298

Comment 4: In addition, there is a very strong review written in the Mayo Clinic Proceedings: Overview of Lymphedema for Physicians and Other Clinicians: A Review of Fundamental Concepts. Manrique OJ, Chen HC., which is very complete and should also be included.

Reply 4: Thank you for sharing this comprehensive review paper. It highlights many of the concepts presented and included a relevant definition for patients with LE that has been included in the revised manuscript.

Changes in the text: Page 8, Lines 188-191

Comment 5: The only are of concern and that a more cautious approach should be made is to mention that LYMPHA is a great operation, as now, several papers have shown that is not. Otherwise I think is a great review article.

Reply 5: Thank you for highlighting the active and animated scientific debate on prophylactic lymphatic procedures. The edited manuscript has been edited to include more heterogenous studies that emphasize to the readership that long-term prospective are still needed before drawing any definitive conclusions.

Changes in the text: Page 19, Lines 665-679

Reviewer B

Thank you for letting me read this comprehensive review of lymphoedema. It gives a good overview of the current scientific base and summarises well international praxis and standards. It is well written and I only have two minor comments:

Comment 1: Under risk factors and under the presentation of prophylactic surgery please include discussion and information regarding "anatomical variations of the lymphatic system" as risk/protective factor to consider also as a potential indication for prophylactic interventions (eg Caplan/Tricipital pathways)

Reply 1: Thank you for pointing out this relevant concept. The edited manuscript has been updated to include a discussion of accessory lymphatic pathways.

Changes in the text: Page 9, Line 223-234

Comment 2: Ref. 142 first author spells his name AA Maldonado (not Mardonado).

Reply 2: Thank you for the correction. Edited accordingly.

Changes in the text: Page 31, Line 1104