



Lymph node transplantation in the management of post-mastectomy lymphedema: a systematic review with meta-analysis

Transplante linfonodal no manejo do linfedema pós-mastectomia: revisão sistemática com metanálise

RAFAEL VILELA EIRAS RIBEIRO^{1,2*} 
LUCIO HENRIQUE ROMÃO DOS
SANTOS-JÚNIOR³ 
IRENE DAHER BARRA^{1,4} 

■ ABSTRACT

This study aimed to analyze, through a systematic literature review with meta-analysis, the success rates of the use of autologous lymph node transplantation for the management of upper limb lymphedema in mastectomized patients, regarding the reduction of excessive volume in the affected limb. The most relevant studies originally published and indexed in any language until August 2019 were analyzed, in the US National Library of Medicine, Cochrane Central Register of Controlled Trials, Web of Science, and Scientific Electronic Library Online databases. The sample consisted of 10 publications that met the established inclusion and exclusion criteria, including 194 patients with 50.0 years average age, being followed up for 31.7 months average. Most patients had the right upper limb affected by lymphedema (58.1%), with symptoms that started more than a year before lymph node transplant surgery (86.4%). Only four patients (2.6%) did not undergo lymphadenectomy during the treatment of breast cancer. Lymph node transplantation provided an average reduction of 52.18% in the excessive volume presented by patients in the limb due to lymphedema. Most of the patients surveyed had a volume reduction higher than 50%. It is concluded that autologous lymph node transplantation is a good option for the management of lymphedema related to breast cancer, providing a considerable reduction in the excessive volume of the affected limb.

Keywords: Mastectomy; Autologous transplantation; Lymph nodes; Lymphedema related to breast cancer; Meta-analysis

Institution: Private Clinic, Juiz de Fora, MG, Brazil.

Article received: September 30, 2019.
Article accepted: December 16, 2019.

Conflicts of interest: none.

DOI: 10.5935/2177-1235.2020RBCP0059

¹ Sociedade Brasileira de Cirurgia Plástica, São Paulo, SP, Brazil.

² Private Clinic, Juiz de Fora, MG, Brazil.

³ Faculty of Medicine of ABC, São Paulo, SP, Brazil.

⁴ Hospital Souza Aguiar, Rio de Janeiro, RJ, Brazil.

■ RESUMO

Este estudo teve o objetivo de analisar, por meio de uma revisão sistemática da literatura com metanálise, os índices de sucesso do uso do transplante autólogo de linfonodos para o manejo do linfedema de membros superiores em pacientes mastectomizadas, quanto à redução do volume excessivo no membro acometido. Foram analisados os mais relevantes estudos publicados originalmente em qualquer idioma até agosto de 2019, indexados às bases de dados *US National Library of Medicine*, *Cochrane Central Register of Controlled Trials*, *Web of Science* e *Scientific Electronic Library Online*. A amostra foi composta por 10 publicações que se adequaram aos critérios de inclusão e exclusão estabelecidos, incluindo 194 pacientes, as quais apresentaram idade média de 50,0 anos, sendo acompanhadas por, em média, 31,7 meses. A maioria das pacientes apresentou o membro superior direito acometido pelo linfedema (58,1%), iniciando os sintomas há mais de um ano prévio à cirurgia de transplante de linfonodos (86,4%). Apenas quatro pacientes (2,6%) não foram submetidas à linfadenectomia durante o tratamento do câncer de mama. O transplante de linfonodos foi capaz de prover uma redução média de 52,18% no volume excessivo apresentado pelas pacientes no membro em decorrência do linfedema, sendo que, a maior parte das pacientes pesquisadas apresentaram redução de volume maior do que 50%. Conclui-se que o transplante autólogo de linfonodos se apresenta como uma boa opção para o manejo do linfedema relacionado ao câncer de mama, proporcionando considerável redução no volume excessivo do membro acometido.

Descritores: Mastectomia; Transplante autólogo; Linfonodos; Linfedema relacionado a câncer de mama; Metanálise.

INTRODUCTION

Breast cancer is one of the leading public health problems in Brazil¹, and, very often, it requires the surgical procedure as one of the methods for its treatment². However, one of the most frequent complications in the postoperative period of breast cancer is lymphedema, a chronic condition caused by the accumulation of fluid rich in proteins in the interstitial space³⁻⁶, whose development can occur immediately after surgery, in rare cases, or years after the treatment⁶⁻¹⁰.

The main risk factors for the development of lymphedema after mastectomy are lymphadenectomy and/or axillary radiation therapy, obesity, and invasive procedures performed on the limb homolateral to breast cancer^{11,12}. Scientific evidence has shown that mastectomy performance associated with immediate breast reconstruction can be a safe and effective method to reduce the risk of developing lymphedema¹³.

However, the occurrence of lymphedema related to breast cancer is still a reality in the routine medical clinic¹³⁻²⁵. To solve this occurrence, the technique of

autologous transplantation of vascularized lymph nodes has been used, aiming to restore the function of the lymphatic system and interrupt the vicious cycle that causes its destruction and the progression of lymphedema^{14-19,21,23-26}. However, the literature is still scarce about research that shows the success rates of using this technique in patients who developed lymphedema after mastectomy.

OBJECTIVE

This study aimed to analyze, through a systematic literature review with meta-analysis, the success rates of the use of autologous lymph node transplantation for the management of upper limb lymphedema in mastectomized patients, regarding the reduction of excessive volume in the limb affected.

METHODS

A methodology based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA)²² was used for systematic reviews. The most

relevant studies originally published and indexed in any language until August 2019 were analyzed in the US National Library of Medicine (PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and Scientific Electronic Library Online databases (SciELO).

To select quality scientific evidence studies, publications were sought for meta-analysis and randomized controlled trials (RCT) in humans without restriction on publication year. The following keywords were used, in different combinations: “lymph node transfer”, “lymph node transplantation”, “lymph node graft”, “lymphedema”, “mastectomy”, “breast cancer surgery”, “postmastectomy” and “cancer.”

The inclusion and exclusion criteria were applied, according to Chart 1.

Chart 1. Inclusion and exclusion criteria for publications.

Inclusion criteria	
Design	<ul style="list-style-type: none"> • RCT • Meta-analysis • Case series
Sample	<ul style="list-style-type: none"> • Human
Intervention	<ul style="list-style-type: none"> • Autologous lymph node transplantation in mastectomized patients who developed lymphedema
Publication period	<ul style="list-style-type: none"> • Not specified
Language	<ul style="list-style-type: none"> • Not defined
Exclusion criteria	
Design	<ul style="list-style-type: none"> • Methodology poorly explained and/or incomprehensible • Case report • Literature review
Publication form	<ul style="list-style-type: none"> • Only abstract

RCT: Randomized Controlled Trials.

At first, the selection of publications was made by analyzing the title, and summary of studies obtained as search results (step 1), followed by the elimination of duplicate results obtained in the different databases searched (step 2). Subsequently, the full version of the publications was read, and the inclusion and exclusion criteria were applied (step 3), aiming to establish the final selection of publications to be included in this research sample, according to the method used in Ribeiro's study in 2019¹³.

In the publications that were part of the sample of this study, data were collected regarding sample size, mean age and patient follow-up, limb affected by lymphedema, previous period of presentation of symptoms, whether or not lymphadenectomy was performed during cancer treatment, in addition to the reduced volume percentage in the limbs affected by

lymphedema. Studies like the one by Gharb et al., in 2011¹⁸, were excluded because, despite having a similar objective to this research, the percentages of reduction in circumference, perimeter, or volume in the limb affected by lymphedema in patients were not defined.

The collected data were submitted to a meta-analysis to formulate the results of this research, using the SPSS for Windows 15 software (IBM SPSS Software, New York, USA)

RESULTS

Searches in different databases resulted in 2,490 publications, which were reduced to 57 after the first stage of analysis (title and summary), 26 after the second stage (removal of duplicates) and, finally, 10 publications after the third stage (analysis of the full content of the articles), which fit the established inclusion and exclusion criteria.

Regarding the ten studies included in this meta-analysis sample, eight are specifically related to the results of autologous lymph node transplantation for the management of post-mastectomy upper limb lymphedema^{14,15,19-21,23-26}, while one compared these findings with the findings of patients undergoing only physical therapy¹⁷.

The publications included in this sample included 194 patients, who had 50.0 years average age, being followed up for 31.7 months average (Table 1).

As shown in Table 2, most patients presented the right upper limb affected by lymphedema (58.1%), beginning the symptoms more than a year before the lymph node transplantation surgery (86.4%). Only four patients (2.6%) did not undergo lymphadenectomy during the treatment of breast cancer.

Table 1. General characteristics of the sample.

Study	Sample (n)	Average age (years)	Average follow-up (months)
Becker et al. ²⁶	24	58.7	99
Becker et al. ¹⁴	6	60.5	21
Lin et al. ²⁰	13	50.7	56.3
Saaristo et al. ²⁵	9	50	6
Cheng et al. ¹⁵	10	53.3	39.1
Nicoli et al. ²⁴	10	54.6	6
Dionyssiou et al. ¹⁷	18	47.7	18
Gratzon et al. ¹⁹	50	12	-
Liu et al. ²¹	30	60	22.1
Montag et al. ²³	24	52.8	18
Total	194	-	-
Average	-	50.0	31.7

Legend: n = number; - = data not specified in the publication.

In general, lymph node transplantation was able to provide an average reduction of 52.18% in the excessive volume presented by patients in the limb as a result of lymphedema; in fact, most of the patients surveyed had a volume reduction higher than 50% (Table 3).

DISCUSSION

One of the factors that have motivated new research involving women undergoing breast cancer treatment is the occurrence of lymphedema in patients who undergo mastectomy^{4-6,11,27,28}, not yet being established all the etiological factors for such occurrence. Anyway, it is recognized that axillary lymph node dissection is a risk factor for the development of lymphedema after mastectomy^{6,11-13,29}, regardless of the surgical technique (simple mastectomy associated with axillary lymph node dissection or modified

radical mastectomy)²⁹. In this study, it was found that the majority of patients included in the sample underwent lymphadenectomy (97.4%), which may have contributed to the development of upper limb lymphedema after treatment for breast cancer.

Therefore, even though many experts have sought risk and preventive factors, the occurrence of lymphedema after a mastectomy is still a reality in clinical practice^{13-21,23-26}, causing a loss in patients' quality of life who develop it. Thus, lymph node transplantation has been used as one of the forms of treatment, improving lymphatic drainage from an affected limb in patients with damaged lymph nodes or hypoplastic lymphatic vessels¹⁶. Therefore, this study aimed to identify the rates of excessive volume reduction caused by lymphedema in the upper limbs of mastectomized patients submitted to autologous lymph node transplantation.

Table 2. Characteristics related to lymphedema presented by the patients.

Study	Affected limb		Symptoms		Lymphadenectomy	
	Right	Left	≤ 1 year	> 1 year	Yes	No
Becker et al. ²⁶	14	10	6	18	24	0
Becker et al. ¹⁴	3	3			6	0
Lin et al. ²⁰	9	4	4	9	11	2
Saaristo et al. ²⁵	-	-	2	7	9	0
Cheng et al. ¹⁵	-	-	0	10	-	-
Nicoli et al. ²⁴	-	-	-	-	-	-
Dionyssiou et al. ¹⁷	-	-	-	-	-	-
Gratzon et al. ¹⁹	27	23	-	-	48	2
Liu et al. ²¹	-	-	0	30	30	0
Montag et al. ²³	15	9	3	21	24	0
Total %	68	49	15	95	152	4
	58.1%	41.9%	13.6%	86.4%	97.4%	2.6%

Legend: ≤ = less than or equal to; > = greater than; % = percentage; - = data not specified in the publication.

Table 3. General characteristics of patients undergoing mastectomy associated with immediate reconstruction.

Study	Reduction of abnormal limb volume				
	Total	> 50%	≤ 50%	No reduction	Average (%)
Becker et al. ²⁶	10	6	6	2	-
Becker et al. ¹⁴	2	3	0	1	-
Lin et al. ²⁰	0	9	3	1	50.55
Saaristo et al. ²⁵	0	3	4	2	-
Cheng et al. ¹⁵	0	4	6	0	40.4
Nicoli et al. ²⁴	-	-	-	-	91.5
Dionyssiou et al. ¹⁷	0	13	5	0	57
Gratzon et al. ¹⁹	-	-	-	-	58.68
Liu et al. ²¹	0	15	6	9	47.06
Montag et al. ²³	-	-	-	-	20.1
Total	12	53	30	15	-
%	10.9%	48.2%	27.3%	13.6%	52.18

Legend: ≤ = less than or equal to; > = greater than; % = percentage; - = data not specified in the publication.

It is recognized that the association of mastectomy with immediate breast reconstruction can prevent the occurrence of post-mastectomy lymphedema^{13,27,30,31}. In this context, a study was found that evaluated the performance of lymph node transplantation simultaneously with breast reconstruction, concluding that this is a useful technique. It caused lymphatic recovery in 83.3% of the patients, without the need for additional posterior surgery, since the procedure had been performed in an associated manner²⁵.

Lymph node transplantation has been emphasized as a considerably effective method, especially when analyzing a study that compares patients who are treated only with physiotherapy and medications (reaching rates of 18% reduction in the volume of the affected limb), with patients undergoing the surgical procedure, of lymph node transplantation, which presented around 57%¹⁷. In general, the findings of this study corroborate the referred research, since it showed that the average percentage of reduction in volume was 52.18% and that most patients had more than half of the excessive circumference reduced after the transplant lymph node. Such findings encourage the indication of the technique since this represents a considerable reduction in the arms discrepancy presented by women with lymphedema and relief in the physical, social, and psychological symptoms of these patients.

It is important to note that, in the case of autologous transplants, lymph node donor sites may be compromised in the event of inadequate collection procedures, which could further aggravate patients' situations for whom solutions are sought. In the study by Demiri et al., in 2018¹⁶, 1.6% (n = 3/189) of the patients developed lymphedema in the lymphatic flap's lower limb donor. In the study by Viitanen et al., in 2012³², although none of the patients developed lymphedema at the donor site, the first post-surgical lymphoscintigrams indicated the need to reduce surgical trauma during the collection of the lymphatic flap. Thus, the importance of a detailed study about each case is mentioned here so that the decision making about the procedures to be adopted is duly based, in particular, on scientific evidence.

It is essential to mention that the technical and scientific evolution makes lymph node transplantation promising, especially when considering its association with other techniques. As an example, it is mentioned that the research presented the highest average percentage of excessive volume reduction in the limb affected by lymphedema in this study by Nicoli et al., in 2015²⁴ (91.5%), in which lymph node transplantation was associated with laser liposuction, enhancing the results and causing a more satisfactory immediate prognosis.

Finally, the need to conduct further research with the focus on the success rates of lymph node transplants for the management of lymphedema related to breast cancer is emphasized, especially with standardized methodologies and testing the associations with methods and technologies that can favor the results and improve the patients' quality of life.

CONCLUSION

Considering the systematic review and meta-analysis carried out, it is concluded that autologous lymph node transplantation is a good option for the management of lymphedema related to breast cancer, providing a considerable reduction (52.18%) in the excessive volume of the affected limb.

COLLABORATIONS

- RVER** Analysis and/or data interpretation, Conception and design study, Data Curation, Final manuscript approval, Methodology, Realization of operations and/or trials, Supervision, Writing - Original Draft Preparation
- LHRSJ** Conception and design study, Writing - Review & Editing
- IDB** Final manuscript approval, Supervision

REFERENCES

1. Instituto Nacional do Câncer (INCA). Estimativa 2018: incidência de câncer no Brasil [Internet]. Rio de Janeiro (RJ): INCA; 2017; [acesso em 2018 Jul 14]. Disponível em: <http://www.inca.gov.br/estimativa/2018/estimativa-2018.pdf>
2. Lyman GH, Somerfield MR, Bosserman LD, Perkins CL, Weaver DL, Giuliano AE. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2017 Feb;35(5):561-4.
3. Ahmed RL, Thomas W, Yee D, Schmitz KH. Randomized controlled trial of weight training and lymphedema in breast cancer survivors. *J Clin Oncol*. 2006 Jun;24(18):2765-72.
4. Buchholz TA, Avritscher R, Yu TK. Identifying the "sentinel lymph nodes" for arm drainage as a strategy for minimizing the lymphedema risk after breast cancer therapy. *Breast Cancer Res Treat*. 2009;116(3):539-41.
5. Demark-Wahnefried W, Campbell K, Hayes SC. Weight management and its role in breast cancer rehabilitation. *Cancer*. 2012 Abr;118(8 Supl):2277-87.
6. Lee KT, Bang SI, Pyon JK, Hwang JH, Mun GH. Method of breast reconstruction and the development of lymphoedema. *Br J Surg*. 2017;104(3):230-7.
7. Gartner R, Jensen MB, Kronborg L, Ewertz M, Kehlet H, Kroman N. Self-reported arm-lymphedema and functional impairment after breast cancer treatment—a nationwide study of prevalence and associated factors. *Breast*. 2010 Dez;19(6):506-15.
8. Lee HD, Ahn SG, Lee SA, Lee HM, Jeong J. Prospective evaluation of the feasibility of sentinel lymph node biopsy in breast cancer patients with negative axillary conversion after neoadjuvant chemotherapy. *Cancer Res Treat*. 2014;47(1):26-33.

9. Miller CL, Colwell AS, Horick N, Skolny MN, Jammallo LS, O'Toole JA, et al. Immediate implant reconstruction is associated with a reduced risk of lymphedema compared to mastectomy alone: a prospective cohort study. *Ann Surg.* 2016 Feb;263(2):399-405.
10. Pandey RA, Shrestha S. Prevalence of arm lymphedema among patients with breast cancer surgery. *JCMS Nepal.* 2016;12(3):111-7.
11. Bevilacqua JL, Kattan MW, Changhong Y, Koifman S, Mattos IE, Koifman RJ, et al. Nomograms for predicting the risk of arm lymphedema after axillary dissection in breast cancer. *Ann Surg Oncol.* 2012 Ago;19(8):2580-9.
12. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. *Lancet Oncol.* 2013 Mai;14(6):500-15.
13. Ribeiro RVE. Prevalência de linfedema após mastectomia em portadoras de câncer de mama: uma revisão sistemática acerca da influência da reconstrução imediata. *Rev Bras Cir Plást.* 2019;34(1):113-9.
14. Becker C, Pham DN, Assouad J, Badia A, Foucault C, Riquet M. Postmastectomy neuropathic pain: results of microsurgical lymph nodes transplantation. *Breast.* 2008 Abr;17(5):472-6.
15. Cheng MH, Chen SC, Henry SL, Tan BK, Lin MC, Huang JJ. Vascularized groin lymph node flap transfer for postmastectomy upper limb lymphedema: flap anatomy, recipient sites, and outcomes. *Plast Reconstr Surg.* 2013 Jun;131(6):1286-98.
16. Demiri E, Dionysiou D, Tsimponis A, Goula OC, Miotalothridis P, Pavlidis L, et al. Donor-site lymphedema following lymph node transfer for breast cancer-related lymphedema: a systematic review of the literature. *Lymphat Res Biol.* 2018 Feb;16(1):2-8.
17. Dionysiou D, Demiri E, Tsimponis A, Sarafis A, Mpalaris V, Tatsidou G, et al. A randomized control study of treating secondary stage II breast cancer-related lymphoedema with free lymph node transfer. *Breast Cancer Res Treat.* 2016 Feb;156(1):73-9.
18. Gharb BB, Rampazzo A, Spanio di Spilimbergo S, Xu ES, Chung KP, Chen HC. Vascularized lymph node transfer based on the hilar perforators improves the outcome in upper limb lymphedema. *Ann Plast Surg.* 2011 Dez;67(6):589-93.
19. Gratzon A, Schultz J, Secrest K, Lee K, Feiner J, Klein RD. Clinical and psychosocial outcomes of vascularized lymph node transfer for the treatment of upper extremity lymphedema after breast cancer therapy. *Ann Surg Oncol.* 2017 Jun;24(6):1475-81.
20. Lin CH, Ali R, Chen SC, Wallace C, Chang YC, Chen HC, et al. Vascularized groin lymph node transfer using the wrist as a recipient site for management of postmastectomy upper extremity lymphedema. *Plast Reconstr Surg.* 2009 Abr;123(4):1265-75.
21. Liu HL, Pang SY, Lee CC, Wong MM, Chung HP, Chan YW. Orthotopic transfer of vascularized groin lymph node flap in the treatment of breast cancer-related lymphedema: clinical results, lymphoscintigraphy findings, and proposed mechanism. *J Plast Reconstr Aesthet Surg.* 2018 Jul;71(7):1033-40.
22. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009 Jul;6(7):e1000097.
23. Montag E, Okada AY, Arruda EGP, Fonseca AS, Bromley M, Munhoz AM, et al. Influence of vascularized lymph node transfer (VLNT) flap positioning on the response to breast cancer-related lymphedema treatment. *Rev Col Bras Cir.* 2019 Mai;46(2):e2156.
24. Nicoli F, Constantinides J, Ciudad P, Sapountzis S, Kiranantawat K, Lazzeri D, et al. Free lymph node flap transfer and laser-assisted liposuction: a combined technique for the treatment of moderate upper limb lymphedema. *Lasers Med Sci.* 2015 Mar;30(4):1377-85.
25. Saaristo AM, Niemi TS, Viitanen TP, Tervala TV, Hartiala P, Suominen EA. Microvascular breast reconstruction and lymph node transfer for postmastectomy lymphedema patients. *Ann Surg.* 2012 Mar;255(3):468-73.
26. Becker C, Assouad J, Riquet M, Hidden G. Postmastectomy lymphedema: long-term results following microsurgical lymph node transplantation. *Ann Surg.* 2006 Abr;243(3):313-5.
27. Avraham T, Daluvoy SV, Riedel ER, Cordeiro PG, Van Zee KJ, Mehrara BJ. Tissue expander breast reconstruction is not associated with an increased risk of lymphedema. *Ann Surg Oncol.* 2010;17(11):2926-32.
28. Crosby MA, Card A, Liu J, Lindstrom WA, Chang DW. Immediate breast reconstruction and lymphedema incidence. *Plast Reconstr Surg.* 2012 Mai;129(5):789e-95e.
29. Park JH, Lee WH, Chung HS. Incidence and risk factors of breast cancer lymphoedema. *J Clin Nurs.* 2008 Jun;17(11):1450-9.
30. Card A, Crosby MA, Liu J, Lindstrom WA, Lucci A, Chang DW. Reduced incidence of breast cancer-related lymphedema following mastectomy and breast reconstruction versus mastectomy alone. *Plast Reconstr Surg.* 2012 Dez;130(6):1169-78.
31. Lee KT, Mun GH, Lim SY, Pyon JK, Oh KS, Bang SI. The impact of immediate breast reconstruction on post-mastectomy lymphedema in patients undergoing modified radical mastectomy. *Breast.* 2013;22(1):53-7.
32. Viitanen TP, Mäki MT, Seppänen MP, Suominen EA, Saaristo AM. Donor-site lymphatic function after microvascular lymph node transfer. *Plast Reconstr Surg.* 2012;130(6):1246-53.

***Corresponding author:**

Rafael Vilela Eiras Ribeiro

Avenida Itamar Franco, 4001/718 Leste, Centro Empresarial Monte Sinai, Bairro Dom Bosco, Juiz de Fora, MG, Brazil.

Zip Code: 36033-318

E-mail: vilelaeiras@hotmail.com