

Manual Lymph Drainage in Cancer Patients: What is the Scientific Evidence and Clinical Recommendations?

doi: <https://doi.org/10.32635/2176-9745.RBC.2021v67n1.1055>

Drenagem Linfática Manual em Pacientes Oncológicos: Quais as Evidências Científicas e as Recomendações Clínicas?

Drenaje Linfático Manual en Pacientes Con Cáncer: ¿Cuál es la Evidencia Científica y las Recomendaciones Clínicas?

Anke Bergmann¹; Jaqueline Munaretto Timm Baiocchi²; Samantha Karlla Lopes de Almeida Rizzi³; Ruy Gonzalo Martinez Allende⁴

INTRODUCTION

Cancer is an important health public problem worldwide. In 2020 in Brazil, 450 thousand new cases were estimated (excluding non-melanoma skin cancer), prostate cancer being the most frequent among men (29.2%) and breast cancer (29.7%) in women¹. Because of the epidemiological transition and population ageing mainly, it is anticipated an increase of more than 70% of cancer cases in Brazil in 2040². However, because of the incorporation of new therapeutics of oncologic treatment, many patients survive cancer. According to data available from Globocan², approximately 1.2 million cancer survivors were estimated in 2018 (prevalent cases). Therefore, it is primordial to establish conducts that favor not cure alone, but also the quality of life of cancer survivors.

The role of the lymphatic system in the immune function and cancer spread is being widely investigated. The neoplastic commitment of the lymph nodes is the most common site of solid tumors metastases and is an important prognostic and therapeutic marker³. The local treatment of solid tumors with surgery and/or radiotherapy involves the approach of the regional lymph nodes somehow and the resulting damage of this system. In addition, systemic treatment (chemotherapy, hormone therapy and/or target-therapy) can collaborate too for the increase of the lymphatic load and reduction of lymphatic transportation, increasing the risk of development of lymphatic complications due to the oncologic treatment.

In this sense, oncologic patients have high incidence of edemas, lymphedemas, deep venous thrombosis and other alterations as the axillary web syndrome, pain and complications of operative wound that can be related with the worsening of the quality of life of this population too³⁻⁸.

The physiotherapy in oncologic patients promotes actions of prevention, diagnosis, recovery, and rehabilitation during the phases of cancer treatment through the use of several physiotherapeutic techniques, resources and conducts⁹. Among them manual therapy is being widely utilized through manual lymph drainage – MLD.

MLD consists in a specific manual therapy performed over the superficial lymphatic system through precise, light, soft and rhythmic maneuvers which follow the anatomy and physiology of the lymphatic system. Its finality is to promote the improvement of the absorption of the liquid and protein of the interstice of the lymphatic capillaries, of the contractility of the lymphatic collectors and absorption of the liquid of the lymph nodes, thus increasing the quantity of liquid returning to the venous system through the lymphatic system¹⁰. In addition, for being maneuvers involving the superficial touching, MLD may also promote improvements to the quality of life and pain reduction, anxiety, nausea, and other symptoms resulting from cancer and its treatment¹¹.

However, MLD, in clinical practice and in graduation courses started to be used indiscriminately and disregarding the evidence-based practices (better scientific evidence, clinical experience and preferences and patient expectations) quite often.

In this context, this article has the objective of discussing the application of MLD for complications resulting from prevention and treatment of oncologic interventions and evolution of cancer. It is expected that this opinion article may contribute for the decision of the physiotherapist in applying or not MLD in each practical situation.

¹National Cancer Institute José Alencar Gomes da Silva (INCA). Coordination of Research. Division of Clinical Research. Rio de Janeiro (RJ), Brazil. E-mail: abergmann@inca.gov.br. Orcid iD: <https://orcid.org/0000-0002-1972-8777>

²Instituto Oncofisio. São Paulo (SP), Brazil. E-mail: jaqueline@oncofisio.com.br. Orcid iD: <https://orcid.org/0000-0001-5477-1634>

³Federal University of São Paulo. Hospital São Paulo. São Paulo (SP), Brazil. E-mail: samantha.rizzi@unifesp.br. Orcid iD: <https://orcid.org/0000-0002-5969-9499>

⁴Universidad Autónoma de Barcelona (UAB). Centro Vodder Argentina. Buenos Aires, Argentina. E-mail: ruymartinezallende@mac.com. Orcid iD: <https://orcid.org/0000-0003-2916-1572>

Corresponding author: Anke Bergmann. Rua André Cavalcanti, 37 – Centro. Rio de Janeiro (RJ), Brazil. CEP 20231-050. E-mail: abergmann@inca.gov.br



DEVELOPMENT

MLD FOR THE PREVENTION OF CANCER TREATMENT-RELATED SECONDARY LYMPHEDEMA

Lymphedema is one of the major complications of oncologic treatment. Preventive MLD, post lymphadenectomy, aims to conduct the superficial lymphatic fluid to the non-compromised regions utilizing the lymph lymphatic anastomoses, mainly the axilla-axillary, axilla inguinal, inguinal-inguinal, called “watershed”¹².

A clinical trial with 106 Brazilian women submitted to surgical treatment for breast cancer assigned to two groups was conducted: exercises *versus* MLD. These women were treated twice a week during the first postoperative month. No alteration of the incidence of postoperative complications between the groups in the evaluation conducted 60 days after the surgery¹³, and in the post-30 months evaluation¹⁴ was observed. The authors concluded that both the exercises and MLD are safe and produce similar results when complications occur.

For women post breast cancer, two systematic reviews and meta-analyzes of randomized clinical trials reported benefits of MLD in reducing the risk of lymphedema when compared with patients that did not submit to this conduct^{15,16}.

In relation to lymphedema of lower limbs, a recent randomized clinical trial was carried out with the objective of evaluating the efficacy of the modified complex decongestive physiotherapy for the reduction of risk of secondary lymphedema of the lower limbs after laparoscopy radical hysterectomy with pelvic lymphadenectomy for the treatment of cervical cancer. The participants were randomly divided in intervention group with modified complex decongestive physiotherapy (self MLD, compression sock, guided exercises, and general care) (n=60) or control group (general care) (n=60). The group with complex decongestive physiotherapy had 70% less odds of lymphedema in comparison with control group (OR=0,30; CI 95%; 0.12 to 0.75; p=0.008)¹⁷. The authors did not control the effect of obesity and asymptomatic venous alterations among the groups, in addition of having used the definition of non-usual lymphedema (difference of 2% among the limbs). Therefore, it is not possible to evaluate whether the effect obtained was because of biases introduced in the study or if the effect is due to MLD or other conducts applied which are part of the complex decongestive physiotherapy (compressive meshes and exercises).

Based in the evidences currently available, it is not possible to affirm that MLD is effective in preventing oncologic treatment-related secondary lymphedema. But

when utilized with other physiotherapeutic conducts, it can favor the adherence to preventive guidelines (as exercises, body weight control and infections), the early diagnosis of lymphedema and the control of other oncologic treatment related symptoms.

EFFECTIVENESS OF MLD IN REDUCING THE VOLUME OF THE LIMB IN THE TREATMENT OF CANCER-RELATED SECONDARY LYMPHEDEMA

Complex decongestive therapy is the standard treatment for lymphedema of any origin¹⁸. MLD is one of the components of this treatment program, it is expensive, long and requires skilled therapists. However, the efficacy of MLD it is still unclear in the scientific literature in reducing the volume of the limb with lymphedema.

A randomized clinical trial with Brazilian women with lymphedema post breast cancer was conducted to try to respond to this question, they were divided in two groups: complex decongestive therapy (MLD, compressive bandaging, skincare and active exercises) and complex decongestive therapy without MLD. The two groups presented reduction of the limb volume, but without difference between them¹⁹. Other recent clinical trials reported similar results where differences of the response to the treatment of lymphedema with or without MLD were not observed^{20,21}.

In a systematic review which attempted to evaluate the efficacy and safety of MLD in the treatment of lymphedema post breast cancer, it was concluded that MLD is safe and can offer additional benefits to compressive therapy in reducing the limb volume²². Another systematic review with similar objective concluded that the patients who submitted to MLD maintain the effects of compressive therapy better, improved quality of life and improvement of lymphedema resulting symptoms²³.

In light of the data available at the moment, MLD cannot be considered the main component of lymphedema treatment, but whenever possible, should be applied to minimize the symptoms and increase the adherence to compressive therapy.

MLD IN THE IMPROVEMENT OF QUALITY OF LIFE OF PATIENTS WITH LYMPHEDEMA

To evaluate the impact of MLD over health-related quality of life (HRQoL) of adults with lymphedema or mixed edema, a systematic review of five studies with women with lymphedema post breast cancer was carried out. One study observed improvement of HRQoL, other three, improvement of the well-being feeling, improvement of weight and diminishing of sleeping disorders in groups submitted to MLD²⁴.

Serra-Añó et al.²⁵ investigated the outcome quality of life in two groups of patients, one submitted to MLD

and other treated with myofascial release. Both techniques had increase of HRQoL scores and other treated with myofascial release. Both techniques had increase of HRQoL scores, no statistical difference was detected in the groups.

Another study compared the use of MLD applied by the therapist and lymphatic self-drainage done by the patient together with complex physical therapy. The intragroup analysis showed that HRQoL increased in the end of the treatment and until six months after the end of the treatment in both groups²⁶.

Devoogdt et al.²⁷ compared two groups, one submitted to guidelines and exercises and other to MLD plus exercises. The HRQoL of both groups improved in all the follow up periods investigated (until 60 months).

A review by Cochrane concluded that the heterogeneity of the studies hinders to understand the impact MLD has on HRQoL but points out that no study reported worsening of HRQoL or severe adverse events resulting from MLD²².

MLD FOR THE IMPROVEMENT OF LYMPHEDEMA-INDUCED CUTANEOUS ALTERATIONS

In patients with cancer related secondary lymphedema, progressive deposition of the fibroadipose tissue, increase of the risk of infections and, in rare cases, secondary malignancies related to cancer can occur. Recent studies showed that fibrosis-induced chronic inflammation plays a key role in the physiopathology and the therapeutic response of lymphedema²⁸. The following question is made: MLD can collaborate not only for the reduction of the limb volume but also in the minimization of fibrosis and inflammatory processes resulting from accumulation of interstitial liquid?

In 16 women with post breast cancer lymphedema, nuclear magnetic resonance was performed to evaluate the tissue composition of limbs with and without lymphedema regarding alterations of the tissue microenvironment post MLD. The authors observed reduction of fibrosis areas soon after DLM²⁸.

In another study with patients with lower limbs lymphedema evaluated with ultrasound with manual compression to observe the displacement of interstitial liquid, it was noticed that in the thigh, there was no difference in skin alterations and subcutaneous tissue and after intervention with MLD. In the calf, however, there was reduction of the skin and subcutaneous tissue density post MLD²⁹.

Despite few studies published so far, MLD appears to reduce the areas of lymphostatic fibrosis immediately after its application. Long-term effects were not evaluated.

MLD AS FACTOR OF RISK INCREASE OF RELAPSE AND METASTASIS IN ONCOLOGIC PATIENTS

MLD is part of the physiotherapeutic approach in several clinical situations oncologic patients present, mainly as one of the components of complex decongestive therapy of lymphedema treatment^{8,18}. However, there are reports that, while increasing the absorption of liquid and proteins of the interstice, it could also favor the occurrence of metastasis³⁰.

In a study with 49 individuals with lymphedema of the upper or lower limb with or without cancer in progression, the treatment of lymphedema with MLD did not increase the risk of metastasis and among those with active disease, the condition did not worsen³¹.

Similar result was found in a study with patients with breast cancer after six years of follow up. No risk increase of the disease evolution (relapse and metastasis) while comparing those who submitted or not to MLD was observed³².

Non-systematic reviews published about the theme also concluded that MLD does not increase the risk of neoplastic evolution^{33,34}.

In conclusion, the evolution of the disease occurs because of a proper microenvironment and according to its tumor biology³⁴. There is no evidence, therefore, that MLD has any impact in the increase of risk of relapse and metastasis, it can be applied safely in oncologic patients.

MLD IN IMPROVING SYMPTOMS OF SYSTEMIC TREATMENT

The efficacy of systemic adjuvant therapy is one of the factors associated to the increase of survival of patients with cancer³⁵. However, several side effects of therapeutics can impact the quality of life of patients, among which, hot flushes, emotional and sleep disorders, muscle and articular pain, depression and anxiety^{35,36}.

Keser and Esmer³⁷ evaluated the effect of MLD in pain threshold and tolerance of 20 women and ten men without lymphatic or oncologic dysfunctions. After the application of MLD, patients presented increased pain threshold and tolerance in comparison with the initial evaluation. The study, however, did not have control group and included only healthy individuals³⁷. The manual stimulus in pressure receptors like what is done with massage techniques, increases the vagal activity and reduces the levels of cortisol with positive effect in pain control and reduction of anxiety and depression³⁸.

Listing et al.³⁹ conducted a randomized clinical trial with 86 women with breast cancer whose intervention group received classic massage of 30 minutes twice a week for five weeks, with significant improvement of fatigue reduction and mood disorders in comparison with control group³⁹. A narrative review of the literature

about the effect of therapeutic massage for pain, anxiety, and depression control of oncologic patients in palliative care shows positive effect of massage in the management of these symptoms⁴⁰.

Studies about oncologic patients address massage techniques other than MLD. The therapeutic effect, however, appears to be beneficial for the improvement of the symptoms resulting from adjuvant systemic treatment being a wide field for future investigation with MLD.

MLD IN IMPROVING IMMUNE RESPONSE

It is well known that lymphedema courses with increase of risk of erysipelas. Erysipelas is a dermal infection manifesting as an acute condition of high fever, malaise, chills, and erythematous plaque with well-defined borders^{12,41,42}. What causes this?

Lymphostasis implies in reduction of the lymphatic return, and with it, limitation to recirculation of lymphocytes and return of skin macrophages to the lymph nodes. This would affect the capacity of immune surveillance, diminishing the response capacity and predisposing infection⁴³.

Therefore, MLD, while improving the lymphangiomotricity and lymphostasis could also improve the circulation of lymphocyte and macrophages and consequently, the capacity of immune surveillance, minimizing the risk of erysipelas⁴⁴.

Indirectly, MLD, while improving the well-being and resuming the physical contact with the patient, even as therapy, would also improve the patient's mental conditions and with it, the capacity of immune response^{45,46}.

MLD IN THE REDUCTION OF MORTALITY AND IMPROVEMENT OF SURVIVAL

To the best of our knowledge, there are no studies that evaluated the impact of MLD in reducing mortality and improvement of oncologic patients' survival. However, some available information may generate hypothesis of possible associations of MLD with these outcomes such as:

- Increase of adherence to the oncologic treatment that occurs through the minimization of MLD-produced side effects^{14,47,48}.
- Improvement of HRQoL in patients submitted to MLD because HRQoL is a possible predictor of mortality in oncologic patients⁴⁹⁻⁵¹.
- Favor early detection of local and systemic evolution of the tumor because of the frequent contact with the physiotherapist.
- Improvement of the conditions of immune surveillance and renovation of interstitial liquids contributing to turn conditions of the tumor micro ambient hostile^{45,46}.

CONCLUSION

All the studies report that MLD is a safe conduct the patients accept well. Although scarce scientific evidence about its efficacy in reducing limbs volume exists, MLD has been widely utilized and with favorable results for the improvement of oncologic treatment associated symptoms, of the evolution characteristics of lymphedema, of the HRQoL leading to the improvement of the prognosis of oncologic patients.

The therapeutic decision whether MLD should be applied in oncologic patients must be based in available scientific evidences, individualized clinical conditions, physiotherapist experience, patient's wish, and economic and structural status of the consultation venue.

CONTRIBUTIONS

All the authors contributed for the study conception and/or design, gathering, analysis and interpretation of data, wording, and critical review. The authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

The author Anke Bergmann declares potential conflict of interests for being scientific editor of INCA's Brazilian Journal of Cancerology. The other authors have no conflict of interests.

FUNDING SOURCES

None.

REFERENCES

1. Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2020: incidência de câncer no Brasil [Internet]. Rio de Janeiro: INCA; 2019 [access March 20, 2020 mar 20]. Available from: <https://www.inca.gov.br/publicacoes/livros/estimativa-2020-incidencia-de-cancer-no-brasil>
2. Ferlay J, Laversanne M, Ervik M, et al. Global Cancer Observatory: Cancer Tomorrow [Internet]. Lyon, France: International Agency for Research on Cancer; c1965-2020 [cited 2020 mar 20]. Available from: <https://gco.iarc.fr/tomorrow>
3. Padera TP, Meijer EFJ, Munn LL. The lymphatic system in disease processes and cancer progression. *Annu Rev Biomed Eng.* 2016;18:125-58. doi: <https://doi.org/10.1146/annurev-bioeng-112315-031200>
4. Trugilho IA, Renní MJP, Medeiros GC, et al. Incidence and factors associated with venous thromboembolism

- in women with gynecologic cancer. *Thromb Res.* 2020;185:49-54. doi: <https://doi.org/10.1016/j.thromres.2019.11.009>
5. Macedo FO, Bergmann A, Koifman RJ, et al. Axillary surgery in breast cancer: acute postoperative complications in a hospital cohort of women of Rio de Janeiro, Brazil. *Mastology* 2018;28(2):80-6. doi: <https://doi.org/10.29289/2594539420180000377>
 6. Ribeiro Pereira ACP, Koifman RJ, Bergmann A. Incidence and risk factors of lymphedema after breast cancer treatment: 10 years of follow-up. *Breast.* 2017;36:67-73. doi: <https://doi.org/10.1016/j.breast.2017.09.006>
 7. Oliveira LL, Aguiar SS, Bender PFM, et al. Men have a higher incidence of seroma after breast cancer surgery. *Asian Pac J Cancer Prev.* 2017;18(5):1423-7. doi: <https://doi.org/10.22034/APJCP.2017.18.5.1423>
 8. Fabro EAN, Bergmann A, do Amaral E Silva B et al. Post-mastectomy pain syndrome: incidence and risks. *Breast.* 2012;21(3):321-5. doi: <https://doi.org/10.1016/j.breast.2012.01.019>
 9. Conselho Federal de Fisioterapia e Terapia Ocupacional (BR). Resolução nº 397, de 03 de agosto de 2011. Disciplina a Especialidade Profissional de Fisioterapia Oncológica e dá outras providências [Internet]. *Diário Oficial da União, Brasília, DF; 2011 nov 24.* [access March 20, 2020]. Available from: <https://www.abfo.org.br/legislacao>
 10. Williams A. Manual lymphatic drainage: exploring the history and evidence base. *Br J Community Nurs.* 2010;15(4):S18-S24. doi: <https://doi.org/10.12968/bjcn.2010.15.Sup5.78111>
 11. Tabatabaee A, Tafreshi MZ, Rassouli M, et al. Effect of therapeutic touch in patients with cancer: a literature review. *Med Arch.* 2016;70(2):142-7. doi: <https://doi.org/10.5455/medarh.2016.70.142-147>
 12. Földi M, Földi E, editors. *Földi's textbook of lymphology.* 2nd ed. München, Germany: Urban & Fischer; 2006.
 13. de Oliveira MM, de Rezende LF, do Amaral MT, et al. Manual lymphatic drainage versus exercise in the early postoperative period for breast cancer. *Physiother Theory Pract.* 2014;30(6):384-9. doi: <https://doi.org/10.3109/09593985.2013.876695>
 14. Oliveira MMF, Gurgel MSC, Amorim BJ, et al. Long term effects of manual lymphatic drainage and active exercises on physical morbidities, lymphoscintigraphy parameters and lymphedema formation in patients operated due to breast cancer: a clinical trial. *PLoS One.* 2018;13(1):e0189176. doi: <https://doi.org/10.1371/journal.pone.0189176>
 15. Stuver MM, ten Tusscher MR, Agasi-Idenburg CS, et al. Conservative interventions for preventing clinically detectable upper-limb lymphoedema in patients who are at risk of developing lymphoedema after breast cancer therapy. *Cochrane Database Syst Rev.* 2015;(2):CD009765. doi: <https://doi.org/10.1002/14651858.CD009765.pub2>
 16. Huang TW, Tseng SH, Lin CC, et al. Effects of manual lymphatic drainage on breast cancer-related lymphedema: a systematic review and meta-analysis of randomized controlled trials. *World J Surg Oncol.* 2013;11:15. doi: <https://doi.org/10.1186/1477-7819-11-15>
 17. Wang X, Ding Y, Cai HY, et al. Effectiveness of modified complex decongestive physiotherapy for preventing lower extremity lymphedema after radical surgery for cervical cancer: a randomized controlled trial. *Int J Gynecol Cancer.* 2020;30(6):757-63. doi: <https://doi.org/10.1136/ijgc-2019-000911>
 18. International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2016 Consensus document of the International Society of Lymphology. *Lymphology.* 2016;49(4):170-84.
 19. Bergmann A, da Costa Leite Ferreira MG, de Aguiar SS, et al. Physiotherapy in upper limb lymphedema after breast cancer treatment: a randomized study. *Lymphology.* 2014;47(2):82-91.
 20. Tambour M, Holt M, Speyer A, et al. Manual lymphatic drainage adds no further volume reduction to Complete Decongestive Therapy on breast cancer-related lymphoedema: a multicentre, randomised, single-blind trial. *Br J Cancer.* 2018;119(10):1215-22. doi: <https://doi.org/10.1038/s41416-018-0306-4>
 21. Gradalski T, Ochalek K, Kurpiewska J. Complex decongestive lymphatic therapy with or without vodder II manual lymph drainage in more severe chronic postmastectomy upper limb lymphedema: a randomized noninferiority prospective study. *J Pain Symptom Manage.* 2015;50(6):750-7. doi: <https://doi.org/10.1016/j.jpainsymman.2015.06.017>
 22. Ezzo J, Manheimer E, McNeely ML, et al. Manual lymphatic drainage for lymphedema following breast cancer treatment. *Cochrane Database Syst Rev.* 2015;(5):CD003475. doi: <https://doi.org/10.1002/14651858.CD003475.pub2>
 23. Lasinski BB, McKillip Thrift K, Squire D, et al. A systematic review of the evidence for complete decongestive therapy in the treatment of lymphedema from 2004 to 2011. *PM R.* 2012;4(8):580-601. doi: <https://doi.org/10.1016/j.pmrj.2012.05.003>
 24. Müller M, Klingberg K, Wertli MM, et al. Manual lymphatic drainage and quality of life in patients with lymphoedema and mixed oedema: a systematic review of randomised controlled trials. *Qual Life Res.* 2018;27(6):1403-14. doi: <https://doi.org/10.1007/s11136-018-1796-5>
 25. Serra-Añó P, Inglés M, Bou-Catalá C, et al. Effectiveness of myofascial release after breast cancer surgery in women undergoing conservative surgery and radiotherapy: a randomized controlled trial. *Support Care Cancer.*

- 2019;27(7):2633-41. doi: <https://doi.org/10.1007/s00520-018-4544-z>
26. Bahtiyarca ZT, Can A, Ekşioğlu E, et al. The addition of self-lymphatic drainage to compression therapy instead of manual lymphatic drainage in the first phase of complex decongestive therapy for treatment of breast cancer-related lymphedema: a randomized-controlled, prospective study. *Turk J Phys Med Rehabil.* 2019;65(4):309-17. doi: <https://doi.org/10.5606/tftrd.2019.3126>
 27. Devoogdt N, Geraerts I, Van Kampen M, et al. Manual lymph drainage may not have a preventive effect on the development of breast cancer-related lymphoedema in the long term: a randomised trial. *J Physiother.* 2018;64(4):245-4. doi: <https://doi.org/10.1016/j.jphys.2018.08.007>
 28. Donahue PMC, Crescenzi R, Scott AO, et al. Bilateral changes in deep tissue environment after manual lymphatic drainage in patients with breast cancer treatment-related lymphedema. *Lymphat Res Biol.* 2017;15(1):45-56. doi: <https://doi.org/10.1089/lrb.2016.0020>
 29. Suehiro K, Kakutani H, Nakamura K, et al. Immediate changes to skin and subcutaneous tissue strains following manual lymph drainage in legs with lymphedema. *Ann Vasc Dis.* 2016;9(1):30-4. doi: <https://doi.org/10.3400/avd.oa.15-00093>
 30. Vereecken P, Mathieu A, Laporte M, et al. Spread of melanoma after lymphatic drainage: relaunching the debate. *Int J Clin Pract.* 2003;57(5):444-5.
 31. Flor EM, Flor EM, Flor AM. Manual lymph drainage in patients with tumoral activity. *J Phlebol Lymphology.* 2009;2:13-15.
 32. Hsiao PC, Liu JT, Lin CL, et al. Risk of breast cancer recurrence in patients receiving manual lymphatic drainage: a hospital-based cohort study. *Ther Clin Risk Manag.* 2015;11:349-58. doi: <https://doi.org/10.2147/TCRM.S79118>
 33. Godette K, Mondry TE, Johnstone PA. Can manual treatment of lymphedema promote metastasis?. *J Soc Integr Oncol.* 2006;4(1):8-12.
 34. Vries D, Piller N, Dawson R, et al. Is there a link between LE treatment and breast cancer reoccurrence? *J Lymphoedema.* 2011;6(1):85-6.
 35. Zajączkowska R, Kocot-Kępska M, Leppert W, et al. Mechanisms of chemotherapy-induced peripheral neuropathy. *Int J Mol Sci.* 2019;20(6):1451. doi: <https://doi.org/10.3390/ijms20061451>
 36. Morales L, Neven P, Timmerman D, et al. Acute effects of tamoxifen and third-generation aromatase inhibitors on menopausal symptoms of breast cancer patients. *Anticancer Drugs.* 2004;15(8):753-60. doi: <https://doi.org/10.1097/00001813-200409000-00003>
 37. Keser I, Esmer M. Does Manual lymphatic drainage have any effect on pain threshold and tolerance of different body parts? *Lymphat Res Biol.* 2019;17(6):651-4. doi: <https://doi.org/10.1089/lrb.2019.0005>
 38. Satija A, Bhatnagar S. Complementary therapies for symptom management in cancer patients. *Indian J Palliat Care.* 2017;23(4):468-79. doi: https://doi.org/10.4103/IJPC.IJPC_100_17
 39. Listing M, Reissshauer A, Krohn M, et al. Massage therapy reduces physical discomfort and improves mood disturbances in women with breast cancer. *Psychooncology.* 2009;18(12):1290-9. doi: <https://doi.org/10.1002/pon.1508>
 40. Falkensteiner M, Mantovan F, Müller I, et al. The use of massage therapy for reducing pain, anxiety, and depression in oncological palliative care patients: a narrative review of the literature. *ISRN Nurs.* 2011;2011:929868. doi: <https://doi.org/10.5402/2011/929868>
 41. Zawieja DC. Contractile physiology of lymphatics. *Lymphat Res Biol.* 2009;7(2):87-96. doi: <https://doi.org/10.1089/lrb.2009.0007>
 42. Chakraborty S, Davis MJ, Muthuchamy M. Emerging trends in the pathophysiology of lymphatic contractile function. *Semin Cell Dev Biol.* 2015;38:55-66. doi: <https://doi.org/10.1016/j.semcdb.2015.01.005>
 43. Mak T, Saunders M, Jet B. Primer to the immune response, 2nd ed. London: Elsevier; 2014. Part II, Lymphocyte Recirculation; p. 50.
 44. Mislin H. Die Lymphdrainage als biotechnisches Problem. *Erfahrungsheilkunde.* 1984;9:573-7.
 45. Mizrahi A, Fulder S, Sheinman N, editors. Potentiating health and the crisis of the immune system [Internet]. Boston, MA: Springer; 1997. Chapter, 22. Cool V. Parasympathetic stimulation through the Vodder original Manual Lymphatic Drainage; p. 213-21. doi: https://doi.org/10.1007/978-1-4899-0059-3_22
 46. Ryan TJ. The skin and its response to movement. *Lymphology.* 1998;31(3):128-9.
 47. Zhang L, Fan A, Yan J, et al. Combining manual lymph drainage with physical exercise after modified radical mastectomy effectively prevents upper limb lymphedema. *Lymphat Res Biol.* 2016;14(2):104-8. doi: <https://doi.org/10.1089/lrb.2015.0036>
 48. Cho Y, Do J, Jung S, et al. Effects of a physical therapy program combined with manual lymphatic drainage on shoulder function, quality of life, lymphedema incidence, and pain in breast cancer patients with axillary web syndrome following axillary dissection. *Support Care Cancer.* 2016;24(5):2047-57. doi: <https://doi.org/10.1007/s00520-015-3005-1>
 49. Lee CK, Hudson M, Simes J, et al. When do patient reported quality of life indicators become prognostic in breast cancer?. *Health Qual Life Outcomes.* 2018;16:13. doi: <https://doi.org/10.1186/s12955-017-0834-2>

50. De Aguiar SS, Bergmann A, Mattos IE. Quality of life as a predictor of overall survival after breast cancer treatment. *Qual Life Res.* 2014;23(2):627-37. doi: <https://doi.org/10.1007/s11136-013-0476-8>
51. Hwang TJ, Gyawali B. Association between progression-free survival and patients' quality of life in cancer clinical trials. *Int J Cancer.* 2019;144(7):1746-51. doi: <https://doi.org/10.1002/ijc.31957>

Recebido em 21/5/2020

Aprovado em 22/9/2020