Lymphology 57 (2024) 191-197

A PROSPECTIVE 2 YEAR REVIEW OF LYMPHEDEMA RATES IN BREAST CANCER PATIENTS FOLLOWING MASTECTOMY, AXILLARY CLEARANCE, AND IMMEDIATE FREE FLAP BREAST RECONSTRUCTION

M. Anderson, D. Hamilton, A. Munnoch

Department of Plastic and Reconstructive Surgery and Burns, Ninewells Hospital, Dundee, Scotland, United Kingdom

ABSTRACT

The reported incidence of lymphedema varies greatly among women treated for breast cancer, making counselling for surgery challenging. This study assessed the incidence of lymphedema in patients undergoing mastectomy and free flap reconstruction using robust, quantifiable, and replicable diagnostic criteria. Data on limb circumference, limb volume, and reported symptoms was collected prospectively pre-operatively, post operatively, and at 2 years. All patients undergoing skin sparing mastectomy with axillary node clearance and immediate free tissue breast reconstruction between 2009 and 2018 were included. We followed 113 patients to 2-year follow-up. The prevalence of patients meeting two identifying criteria was highest in the immediate post-operative period at 11%, falling to 4% at 2 years. The proportion of patients meeting three criteria remained static from the post-operative period to two years at 7%, though the incidence declined over that period. All the patients with three identifying criteria post-operatively and at two years had received either chemotherapy or chemotherapy and radiotherapy. Clear diagnostic criteria are important for the accurate assessment and study of post operative lymphedema. It is possible that free tissue transfer could reduce the incidence of or delays the onset of lymphedema in patients undergoing mastectomy and axillary clearance.

Keywords: Breast cancer; Secondary lymphedema; Diagnostic criteria (for lymphedema)

INTRODUCTION

Those undergoing mastectomy for breast cancer face many decisions related to treatment and reconstruction. The wide range of percentage risks of lymphedema after axillary dissection quoted in various studies makes counselling and consenting patients difficult. Innovations in treatment and improved survival rates shift the focus of patients and clinicians towards reducing associated morbidity.

Lymphedema is the chronic accumulation of lymphatic that occurs when part of the lymphatic drainage system fails to work effectively. It can lead to tissue changes, pain, reduced exercise tolerance, recurrent infections, and poor quality of life. The condition is caused by disruption in lymphatic drainage and a buildup of lymph fluid in the tissues. In the literature the likelihood of developing lymphedema after breast cancer is mostly estimated around 20% (1-4), however, diagnostic criteria vary widely. One study quoted a rate as high as 87% at 30 months using a 2cm difference in circumference as the diagnostic criteria (5).

Causes of lymphedema previously discussed have included the extent of surgical dissection and subsequent scarring, radio-

therapy, the presence of superadded infection, and impedance of the axillary vein. Svensson et al demonstrated that within their cohort of patients with chronic arm oedema after breast cancer treatment, 70% of patients had impaired venous outflow (6). Higher rates of sonographic abnormalities within the axillary vein have also been demonstrated in patients with breast cancer related lymphedema (7) and altered flow has been demonstrated within the axillary vein after axillary dissection (8).

One of the main difficulties faced by physicians trying to diagnose and investigate breast cancer-associated lymphedema is the lack of defining criteria. It could, of course, be argued that patient-reported symptoms are the most important factor defining lymphedema, and Fu et al. showed patients reporting three symptoms to be a sensitive and specific marker of lymphedema (9). However, clinical diagnosis combines several factors, and having quantifiable data enables more accurate comparison. The measurement of arm circumference using 10cm interval measurements described by Foroughi is easily replicated with good reliability (10), and limb volume difference is a practical and time-efficient way to assess for lymphedema (11). We have sought to combine these in assessing patients in our study.

METHODS

As a means of monitoring for lymphedema, all patients from 2009 onwards undergoing mastectomy & immediate reconstruction have had limb volumes calculated pre & postoperatively with data stored on an excel database. With institutional approval (from the Caldicott Guardian, Ninewells Hospital Dundee, 2020), those patients who underwent axillary clearance & immediate autologous free flap reconstruction were identified, totalling 210 patients. From this, 198 patients who had full preoperative and postoperative data at 6 months were included, 113 patients had full data available at 2-year follow-up. Details of adjuvant cancer treatment, limb dominance and any lymphedema treatment were noted.

Lymphedema was identified using three recognized criteria: patient-reported symptoms (e.g., swelling/heaviness); >2cm circumferential difference at a fixed point of measurement; and excess volume of ≥10% (limb volume was calculated by measuring limb circumference at 4cm intervals using the modified Frustum method where segment volume = $L/12\pi$ ($C1^2$ + C1 C2 + $C2^2$)

All patients had a skin sparing mastectomy with full axillary clearance, followed by an immediate free tissue breast reconstruction.

RESULTS

Patients ranged in age from 25 to 68 (mean 50); 92% were right-handed and 8% left-handed. Left mastectomies were carried out on 44.4% of patients and right mastectomies on 39% of patients, 17% had bilateral mastectomies.

Patients who underwent axillary node clearance on the side of their dominant hand made up 47% of the group, 53% had surgery on the contralateral side to their dominant hand. Most patients underwent adjuvant treatment; 73% had combination chemotherapy and radiotherapy, 13% had chemotherapy alone and 3% had radiotherapy only. (*Table 1*). Prior to surgery 17% of patients demonstrated at least one identifying criteria, but only 2% met all three. In half of these patients the affected arm was their dominant side (which can be up to 10% larger (13)). The side affected and presence or absence of symptoms did not appear to follow a pattern in this group, however six patients (3%) met none of the criteria at six months and 2 years, suggesting an improvement in their lymphedema after surgery (*Fig. 1*).

The prevalence of those meeting two identifying criteria was highest in the immediate post-operative period at 11%, falling to 4% at 2 years. The proportion of patients meeting three criteria remained static from the post-operative period to two years at 7%, though the incidence declined over that period from 5% to 3% (*Fig. 2*).

All the patients with all three identifying criteria post-operatively and at two years had

TABLE 1
Percentage of Patients Experiencing Symptoms, with Increased Circumference, Increased Limb Volume, and Meeting Two or Three Criteria Pre-Operatively, Post-Operatively, and at Two Years According to Adjuvant Treatment and Side of Cancer

	Pre-Operative Assessment				
	Symptoms	Circumference	VDiff	2 criteria	3 criteria
Chemotherapy	4%	4%	4%	0%	4%
Radiotherapy	0%	0%	0%	0%	0%
Chemoradiotherapy	3%	11%	7%	3%	1%
No adjuvant treatment	5%	0%	0%	0%	0%
Dominant Side	5%	11%	9%	6%	3%
Non-Dominant Side	1%	7%	3%	1%	1%
	Post-Operative Assessment				
	Symptoms	Circumference	VDiff	2 criteria	3 criteria
Chemotherapy	23%	19%	12%	4%	8%
Radiotherapy	0%	17%	17%	17%	0%
Chemoradiotherapy	27%	23%	14%	10%	8%
No adjuvant treatment	10%	29%	19%	19%	0%
Dominant Side	32%	29%	24%	14%	13%
Non-Dominant Side	17%	16%	8%	9%	2%
	Assessment at 2 years				
	Symptoms	Circumference	VDiff	2 criteria	3 criteria
Chemotherapy	17%	25%	17%	0%	17%
Radiotherapy	0%	0%	0%	0%	0%
Chemoradiotherapy	22%	18%	10%	6%	7%
No adjuvant treatment	38%	0%	0%	0%	0%
Dominant Side	19%	15%	11%	4%	8%
Non-Dominant Side	8%	6%	1%	1%	1%

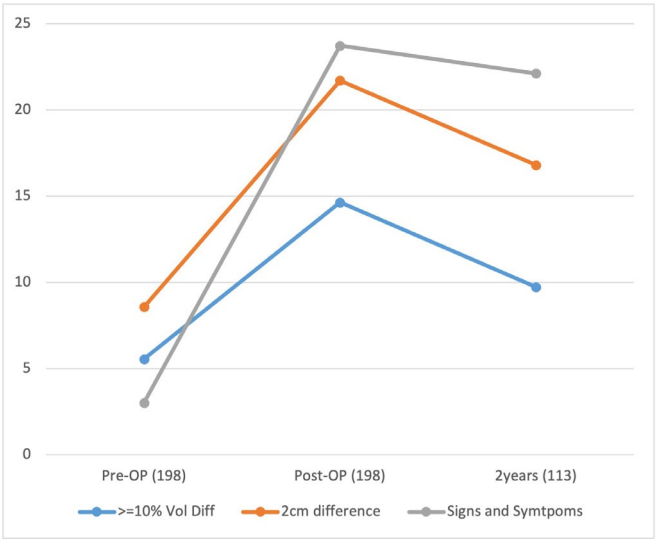

Fig. 1. *The percentage prevalence of criteria used to diagnose lymphedema at the three time points.*

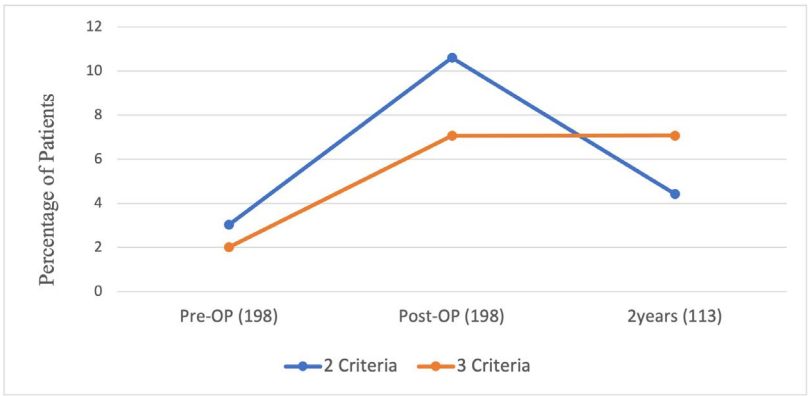

Fig. 2. *The percentage prevalence of patients meeting multiple diagnostic criteria at the three different time points.*

TABLE 2
The Average Number of Criteria Met by Patients Pre-Operatively, Post-Operatively, and at 2 Years by Treatment Modality

Treatment	Average No. Criteria Pre-op	Average No. Criteria Post-Op	Average No. Criteria 2 years
Pressure Garments and Massage	0	2	1
Massage Only	0	0.8	0.8
Pressure Garments Only	0.4	1.8	1
No Treatment	0.2	0.4	0.1

received either chemotherapy or chemotherapy and radiotherapy. The effects of radiotherapy alone appeared to be temporary and had resolved at two years, though this was a small group of patients. Patients who underwent surgery on their dominant side had higher incidences of all criteria at all time points. Treatment with pressure garments appeared to be effective, reducing the average number of criteria met by patients at two years. Treatment with massage alone did not appear to have an effect (*Table 2*).

Patients with evidence of lymphedema at their post-operative review were referred for lymphatic massage and pressure garments. Patients had variable compliance with pressure garments.

DISCUSSION

This study is limited by the exclusion of patients with a BMI >35, however it would be unusual to offer someone with a very high BMI a free flap reconstruction, so this is in line with current practice.

Some variability in limb volume related to hand dominance has been demonstrated by Smoot et al (12). However, we found a small group of patients that experienced symptoms of lymphedema and limb volume and circumference difference pre-operatively. This is in line with previous studies suggesting that there can be significant pre-operative functional differences in the lymphatic system on the affected side (13). In the data presented by Armer and Stewart patients who met lymphedema

criteria pre-operatively were excluded from subsequent analysis (14,15), and once a patient met one criterion it was assumed that the criterion was met at all subsequent time points. Our findings are in stark contrast to those of Armer and Stewart, who demonstrated a steady increase in the incidence of lymphedema to 87% at 2.5years in patients undergoing surgery for breast cancer. Our data suggests that patients undergoing free-flap reconstruction may behave differently; when multiple criteria are combined to identify the presence of lymphedema the persistent rate of lymphedema after mastectomy, axillary clearance and free-flap reconstruction is 7.1%. There may even be a small group of patients for whom surgery with free-flap reconstruction improves their lymphedema, this is in line with previous findings (16-18).

It is possible that our low rate of lymphedema as defined by three criteria reflects a relatively short follow-up time. Menzes et al demonstrated a 33% incidence of lymphedema in women undergoing breast reconstruction (mostly with TRAM flap) and found that the average time to presentation was 93 months, however hand dominance and BMI were not adjusted for and only a single criterion of limb volume difference was used (19). Some studies have not found that reconstruction influences time to presentation (20), however most have demonstrated a significant reduction in incidence as well as later presentation (18,21,22). It should be noted that patient-reported symptoms appeared to be the most sensitive identifying criterion, and it could be argued that it is the most important. The 22% of patients experiencing this at 2 years is a closer figure to those previously reported in patients undergoing reconstruction by Menzes (19). A previously proposed mechanism is that in this group of patients the use of free tissue transfer provides healthy tissue to the axilla, reducing scarring around the axillary vein (23). The presence of vascularized tissue may also allow for growth factors to be released, enabling angiogenesis and lymphatic regeneration (24).

The current mainstay of treatment in our unit is manual decongestive massage with fitted compression garments. This appears to be effective for patients with early signs of lymphedema at postoperative review, and the average number of criteria met by patients at two years is reduced. Patients had variable compliance with compression garments and treatment with massage alone did not appear to have an effect. It is thought that early intervention with external compression garments in the absence of signs or symptoms does not prevent lymphedema in patients undergoing axillary clearance (25), however there are emerging surgical approaches that may be relevant to these patients in the future. Lymph node transfer is one such recognised technique and reports of significant improvement have been made (26-29). The preparation for lymph node transfer involves excision of the scar tissue in the axilla in preparation for transfer of the vascularised lymph node. Scar tissue can impede the flow of lymphatic fluid and it has been shown that the extent of dissection is related to the severity of lymphedema (30) which implicates a role for extent of scarring. It is possible that we demonstrated a relatively low rate of lymphedema after surgery because the transfer of any vascularised tissue prevents formation of scar tissue across the axilla and has a similar effect to transferring lymph nodes (31,32). This merits further exploration as taking donor lymph nodes carries adjacent risks of lymphedema to the donor area (33). If axillary scarring is the primary driver behind upper limb lymphedema following axillary clearance it is possible that other techniques such as fat grafting around the axillary vein may be of benefit (34). In the future it may be possible to identify individuals at higher risk of developing lymphedema and techniques such as reverse arm mapping and prophylactic lymphatic venous anastomosis (35-38) at the stage of axillary clearance may be considered. As alternative oncological approaches to axillary disease emerge, it may be that an emerging conservative approach to axillary surgery causes less scarring and a decrease in lymphedema after surgery may be seen (39).

It has previously been suggested that not only lymphatic but also venous obstruction may be implicated in arm swelling after axillary clearance.

We feel this study has enabled us to provide clearer information for our patient group when discussing their risk of developing lymphedema, however it remains a difficult condition to predict given it often has multiple contributing factors. A further confounding problem is that literature on the subject is often challenging to interpret given the varying diagnostic criteria. Many promising treatment techniques are discussed in the literature to further reduce the risk of developing lymphedema. However, we feel it is important to interpret the results cautiously until there are randomized control trials comparing the treatment modalities with clear diagnostic criteria for lymphedema.

CONFLICT OF INTEREST AND DISCLOSURE

All authors declare no competing financial interests exist.

ACKNOWLEDGMENTS

The authors thank the nursing staff in Ninewells Hospital Dundee for performing the measurements of patients attending outpatient clinics.

REFERENCES

1. Erickson, VS, ML Pearson, PA Ganz, et al: Arm edema in breast cancer patients. J. Natl. Cancer I. 93 (2001), 96–111.
2. DiSipio, T, S Rye, B Newman, et al: Incidence of unilateral arm lymphoedema after breast cancer: A systematic review and meta-analysis. Lancet Oncol. 14 (2013), 500–515.
3. Petrek, J. A. & Heelan, M. C. Incidence of breast carcinoma-related lymphedema. Cancer 83, 2776–2781 (1998).
4. Lee, TS, SL Kilbreath, KM Refshauge, et al: Prognosis of the upper limb following surgery and radiation for breast cancer. Breast Cancer Res. Tr. 110 (2008), 19–37.
5. Armer, JM, BR Stewart: Post-breast cancer lymphedema: Incidence increases from 12 to 30 to 60 months. Lymphology 43 (2010), 118–127.
6. Svensson, WE, PS Mortimer, E Tohno, et al: Colour Doppler demonstrates venous flow abnormalities in breast cancer patients with chronic arm swelling. Eur. J. Cancer 30A (1994), 657–660.
7. de Abreu Junior, GF, GBB Pitta, M Araujo, et al: Ultrasonografic changes in the axillary vein of patients with lymphedema after mastectomy. Rev. Col. Bras. Cir. 42 (2015), 81–92.
8. Pain, SJ, S Vowler, AD Purushotham: Axillary vein abnormalities contribute to development of lymphoedema after surgery for breast cancer. Br. J. Surg. 92 (2005), 311–315.
9. Fu, MR, D Axelrod, CM Cleland, et al: Symptom report in detecting breast cancer-related lymphedema. Breast Cancer 7 (2015), 345–352.
10. Foroughi, N. ES Dylke, RD Paterson, et al: Inter-rater reliability of arm circumference measurement. Lymphat. Res. Biol. 9 (2011), 101–107.
11. De Vrieze, T, N Gebruers, WA Tjalma, et al: What is the best method to determine excessive arm volume in patients with breast cancer-related lymphoedema in clinical practice? Reliability, time efficiency and clinical feasibility of five different methods. Clin. Rehabil. 33 (2019), 1221–1232.
12. Smoot, B., BA Cooper, Y Conley, et al: Differences in limb volume trajectories after breast cancer treatment. J. Cancer Surviv. 10 (2016), 772–782.
13. Rezende, LF, FV Pedras, CD Ramos, et al: Preoperative upper limb lymphatic function in breast cancer surgery. Rev. Assoc. Med. Bras. 57 (1992), 540–544.
14. Armer, JM, et al. Lymphedema symptoms and limb measurement changes in breast cancer survivors treated with neoadjuvant chemotherapy and axillary dissection: Results of American College of Surgeons Oncology Group (ACOSOG) Z1071 (Alliance) substudy. Support Care Cancer 27 (2019), 495–503.
15. Armer, JM, BR Stewart, RP Shook: 30-MONTH POST-BREAST CANCER TREATMENT LYMPHOEDEMA. J. Lymphoedema 4 (2009), 14–18.
16. Blanchard, M., M Arrault, S Vignes: Positive impact of delayed breast reconstruction on breast-cancer treatment-related arm lymphoedema. J. Plast. Reconstr. Aes. 65 (2012), 1060–1063.
17. Card, A., MA Crosby, J Liu, et al: Reduced incidence of breast cancer-related lymphedema following mastectomy and breast reconstruction versus mastectomy alone. Plast. Reconstr. Surg. 130 (2012), 1169–1178.

18. Menezes, MM, et al. Breast reconstruction and risk of lymphedema after mastectomy: A prospective cohort study with 10 years of follow-up. J. Plast. Reconstr. Aes. 69 (2016), 1218–1226.
19. Crosby, MA, A Card, J Liu, et al: Immediate breast reconstruction and lymphedema incidence. Plast. Reconstr. Surg. 129 (2012), 789e–795e.
20. Lee, K-T, G-H Mun, S-Y Lim, et al: The impact of immediate breast reconstruction on post-mastectomy lymphedema in patients undergoing modified radical mastectomy. The Breast 22 (2013), 53–57.
21. Lee, K-T, SI Bang, J-K Pyon, et al: Method of breast reconstruction and the development of lymphoedema. Br. J. Surg. 104 (2017), 230–237.
22. Siotos, C, ME Sebai, EL Wan, et al: Breast reconstruction and risk of arm lymphedema development: A meta-analysis. J. Plast. Reconstr. Aes. 71 (2018), 807–818.
23. Yan, A, T Avraham, JC Zampell, et al: Mechanisms of lymphatic regeneration after tissue transfer. PLOS ONE 6 (2011), e17201.
24. Raju, A, DW Chang: Vascularized lymph node transfer for treatment of lymphedema: A comprehensive literature review. Ann. Surg. 261 (2015), 1013–1023.
25. Ozturk, CN, C Ozturk, M Glasgow, et al: Free vascularized lymph node transfer for treatment of lymphedema: A systematic evidence based review. J. Plast. Reconstr. Aes. 69 (2016), 1234–1247.
26. Scaglioni, MF, M Arvanitakis, Y-C Chen, et al: Comprehensive review of vascularized lymph node transfers for lymphedema: Outcomes and complications. Microsurgery 38 (2018), 222–229.
27. Becker, C, J Assouad, M Riquet, et al: Post-mastectomy lymphedema: Long-term results following microsurgical lymph node transplantation. Ann. Surg. 243 (2006), 313–315.
28. Avraham, T, SV Daluvoy, ER Riedel, et al: Tissue expander breast reconstruction is not associated with an increased risk of lymphedema. Ann. Surg. Oncol. 17 (2010), 2926–2932.
29. Maldonado, AA, R Chen, DW Chang: The use of supraclavicular free flap with vascularized lymph node transfer for treatment of lymphedema: A prospective study of 100 consecutive cases. J. Surg. Oncol. 115 (2017), 68–71.
30. Toyserkani, NM, CH Jensen, S Tabatabaeifar, et al: Adipose-derived regenerative cells and fat grafting for treating breast cancer-related lymphedema: Lymphoscintigraphic evaluation with 1 year of follow-up. J. Plast. Reconstr. Aes. 72 (2019), 71–77.
31. Jørgensen, MG, NM Toyserkani, JA Sørensen: The effect of prophylactic lymphovenous anastomosis and shunts for preventing cancer-related lymphedema: A systematic review and meta-analysis. Microsurgery 38 (2018), 576–585.
32. Penha, TRL, C Ijsbrandy, NAM Hendrix, et al: Microsurgical techniques for the treatment of breast cancer-related lymphedema: A systematic review. J. Reconstr. Microsurg. 29 (2013), 99–106.
33. Campisi, C. C., Ryan, M., Boccardo, F. & Campisi, C. LyMPHA and the Prevention of Lymphatic Injuries: A Rationale for Early Microsurgical Intervention. J. Reconstr. Microsurg. 30 (2014), 71–72.
34. Agarwal, S, RM Garza, DW Chang: Lymphatic Microsurgical Preventive Healing Approach (LYMPHA) for the prevention of secondary lymphedema. Breast J. 26 (2020), 721–724.
35. Co, M, L Lam, D Suen, et al: Axillary reverse mapping in the prevention of lymphoedema: A systematic review and pooled analysis. Clin. Breast Cancer 23 (2023), e14-e19.
36. Schaverien, MV, DA Munnoch: Microvascular breast reconstruction with vascularised lymph node transfer for the management of lymphoedema secondary to axillary surgery for breast cancer. JPRAS 66 (2013), P1007-1008.
37. Beederman, M, DW Chang: Advances in surgical treatment of lymphedema. Arch. Plast. Surg. 48 (2021), 670-677.
38. Deldar, R, D Spoer, N Gupta, et al: Prophylactic lymphovenous bypass at the time of axillary lymph node dissection decreases rates of lymphedema. Ann. Surg. Open 4 (2023), e278.
39. Noguchi, M, M Inokuchi, M Yokoi-Noguchi, et al: Conservative axillary surgery is emerging in the surgical management of breast cancer. Breast Cancer 30 (2023), 14-22.

Meg Anderson
Plastic Surgery Registrar and Chief Resident
Canniesburn Plastic Surgery Unit
Glasgow, United Kingdom
Phone: 07783 433 139
E-mail: megan.anderson@doctors.org.uk