How can we know the true magnitude of any breast cancer-related lymphoedema if we do not know which is the true dominant arm?

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Key words

Breast cancer, grip strength, lymphoedema, true dominance, weakness

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Abstract

Background: Patients with breast cancer tend to limit the use of their arm which may result in muscle reduction and misdiagnosis of breast cancer-related lymphoedema (BCRL). **Aims:** To examine whether patient-reported arm dominance matched the true dominant arm and if the side of surgery had an impact on grip strength and BCRL. **Methods**: Grip strength was used to determine the patients' true dominant arm and assess any muscle weakness. A comparison was made between patients who had surgery on their dominant side and their non-dominant side and between patients who had grip strength weakness in their affected side. **Results:** 31.6% had a higher grip strength in the perceived non-dominant side. There were 39.5% of patients who had weakness in their affected arm. The grip strength weakness of the affected side was shown in 52.9% in who received surgery on reported dominant side, while it was shown in only 28.6% in the patients who received surgery on the non-dominant side. L-Dex® (ImpediMed) was significantly higher in the patients who received surgery on their perceived non-dominant side compared with the patients who received it on their dominant side (p=0.031). The relative oedema volume in the forearm (p=0.000) and whole arm (p=0.003) was significantly higher in the patients who received surgery on their perceived dominant side compared with the patients who received it on their non-dominant side. There was no diferent in skin induration between patients with weakness and non-weakness. **Conclusion:** The patients' reported dominance might be different from true dominance due to treatment side effects or avoidance of using the affected arm. This might affect the diagnosis of BCRL using L-Dex or circumferences of limb.

Healthcare professionals in Japan routinely advise people with breast cancer to avoid exercise and activity involving the arm that is deemed at most risk of lymphoedema. Therefore, many patients limit the use and activity of one of their arms.

However, a recent systematic review showed that exercise for breast cancer-related lymphoedema (BCRL) might be beneficial (Ridner et al, 2012). The study suggests patients should not keep their arm immobile. Based on a new interpretation of Starling's law (Woodcock and Woodcock, 2012), all fluids which leave the vascular system are removed from the tissues by the lymphatics, and the loading of the lymphatic system is reliant primarily on external pressure variation. During activity and movement, lymph loading and flow rely on external pressure variation brought by the extrinsic system (which includes the skeletal muscles as a pumping facilitator) which is more important at rest and when lymph loads are generally lower (Földi, 2012).

Reducing the use of an arm may quickly reduce the muscle mass and limb size. This reduction of the extrinsic tissue pressure due to the loss of sufficient muscle pump may lead to a reduction or even failure of the ability to load the lymphatic capillaries and its movement along the collectors. Skeletal muscle mass will also inevitably reduce if patients are inactive. Trappe et al (2007) showed a 21% muscle volume reduction in the quadriceps and a 29% reduction in the triceps surae muscle occurring in young women after 60 days of bed rest. A study by Lee et al (2015) involving 80 participants showed 36.3% of patients with BCRL had significant handgrip weakness in their affected arm (Lee et al, 2015). The fear of using the affected arm was significantly higher in the patient with weakness rather than patients who did not have a weakened grip. The group with handgrip weakness had received significantly more advice about restricting arm activity (Lee et al, 2015). Patients might have thought that the use of the affected arm can cause BCRL. It is probable that the muscle mass declined through lack of use, and as a consequence, circumferences would also reduce – especially in the fore and upper arm areas where the muscles that are responsible for major arm and hand movement are located.

Another study involving 149 participants (Sato et al, 2014) reported that the grip strength in the group that had educational intervention and had been exercising was

significantly improved after surgery compared with the control group and this suggests that grip strength might decrease if a patient is not motivated by rehabilitation.

By reducing the mobility of their at-risk limb, some patients may have underlying muscle mass reduction and associated reduced limb volume of their affected arm, despite apparent signs of BCRL (Arinaga et al, 2015).

This evidence questions the accuracy of any assessment of the presence or severity of unilateral BCRL where the difference of circumference or volume between arms is the mainstay of lymphoedema estimation. We need to avoid falling into the trap of making an inappropriate diagnosis of BCRL. A consideration and measurement of the possibility of muscle mass change in limbs before and after surgery may help to improve the accuracy of the diagnosis.

Arm dominance is considered to be an important factor in the diagnosis of BCRL (Dylke et al, 2012) as the more dominant arm will usually have larger muscles, and therefore more water, since muscles are 70% water (Paulev and Zubieta-Calleja, 2011).

The grip strength is a simple indirect measure of muscle quality (Mitchell et al, 2012). This can be used to measure muscle strength and function in the limb before and after surgery for breast cancer. As grip strength is generated from the muscles in the forearm, the muscle mass in the forearm is positively associated with grip strength, thus the volume of the forearm will generally be greater if the grip strength is higher (Abe et al, 2015).

Grip strength is a valid and reliable indicator of muscle strength (Mijnarends et al, 2013), and is an interesting indicator for many diseases, including cardiovascular disease and stroke (Newman et al, 2006; Leong et al, 2015). In older people, low grip strength may relate to dependency in activities of daily living and cognitive decline (Taekema et al, 2010).

To determine or evaluate the early stage of unilateral lymphoedema in clinical and research settings, the lymphoedema index (L-Dex®, ImpediMed) has been developed. It uses the extracellular fluid/intracellular fluid (ECF/ICF) ratio between oedematous and contralateral limbs to measure unilateral BCRL (Vicini et al, 2012; Fu et al, 2013; Dylke et al, 2014). The value of L-Dex will be influenced by variation in muscle mass and, in particular, by its reduction. The L-Dex algorithm uses limb dominance as the dominant arm will normally have more muscle and water (Dylke et al, 2012) due to common use in daily life. Therefore, arm dominance is significantly linked to limb volume in people who do not have lymphoedema.

However, there are some cases of reversal where the non-dominant arm or forearm has a larger volume than the self-reported dominant arm (Gebruers et al, 2007). This occurred in 12.8–29.2% of the general population (n=250). Gebruers et al (2007) suggested that the Edinburgh Handedness Inventory (EHI) is the best way to determine left or right-handedness instead of relying on the patient or asking them which hand they write with.

Even though patients with BCRL may tend not to use their affected arm for heavy workloads, they may still think their dominant arm is the one they write with.

It is important to determine the true dominant arm — the one with more muscle — to make an accurate assessment of BCRL, and this may be different from the arm the patient thinks to be their dominant arm. The failure to determine a true dominant arm, which has more muscle, could affect the accuracy of the diagnosis of BCRL using circumference, volume and L-Dex to diagnose. This could help avoid missing 20% of true lymphoedema cases (Fu et al, 2013).

It is essential that we determine the true dominant arm in order to measure and interpret the circumference, volume and L-Dex in arms accurately and to accurately know the extent of the true swelling associated with lymphatic failure.

Aims

This study aims to determine whether the patient's self-reported dominant arm is the same as the true dominant arm (determined by it having more muscle than the contralateral arm) in patients with BCRL. It will also explore the difference between patients who had or who did not have surgery on their reported dominant side, and between patients who have grip strength weakness and no grip strength weakness in their affected hand.

Methods

This is a part of a larger study, the effectiveness of self-care programmes for breast cancer treatment-related lymphoedema randomized pilot study which was approved by the Ethics Committee for Clinical Research in Tohoku University Hospital and other related institutions. The baseline data of these patients were used in this sub analysis.

Patients

The patients were recruited from four institutions in the Tohoku (north-east region) in Japan. The inclusion criteria were:

- Unilateral breast-cancer-treatment-related lymphoedema,
- Oedema limb grade >1 using the common terminology criteria for adverse events (CTCAE) v4
- Finished active treatment more than six months before
- ECOG performance scale 0–2
- Able to answer questionnaires and practice self-care
- Written consent.

The exclusion criteria were:

- Any sign of skin damage or acute inflammation on the affected arm
- Cancer recurrence
- Pregnant or attempting conception
- Cardiac pacemaker or implantable cardioverter-defibrillator.

Determining the true dominant arm

The definition of a true dominant arm is one that has more muscle in the forearm shown by grip strength. To determine the true dominant arm, a Jamar's type handgrip dynamometer (MG4800®, Taiwan) was used to measure the grip strength of both hands. Muscle mass and limb size of the forearm is positively associated with the grip strength (Abe et al, 2015). Although an average of three measures of grip strength is common (Fess, 1982), a report suggests one maximal trial is as reliable and less painful (Coldham et al, 2006). For this reason we measured the grip strength only twice for each hand and then averaged those values to reduce the risk of deterioration of the BCRL.

Comparison of patients who had and who did not have surgery on their reported dominant side

The grip strength and lymphoedema parameters were measured using the L-Dex U400, tissue induration using a tonometer (Biomedical Engineering, Flinders University, Australia), and relative oedema volume were compared between patients who had surgery in their dominant side and non-dominant side. The Mann-Whitney Exact test was used to compare between

variables. The significance level was set at 0.05 and two-tailed tests were used.

Determination of grip strength weakness

We also examined the grip strength weakness of the patient's affected arm. Since the theory that the dominant arm should be 10% stronger rather than the non-dominant arm (Petersen et al, 1989), we defined grip strength weakness in the affected arm as follows:

- If the affected arm is the self-reported dominant arm, the grip strength of the affected arm must be more than the grip strength of the non-dominant arm by 10% or more.
- If the affected arm is the self-reported non-dominant arm, the grip strength of the affected arm must be 10% less than the grip strength of the dominant arm.

These values are called estimated value of grip strength and a lower grip strength than this value indicates grip strength weakness.

Table 1. Demographic and clinical characteristics of participants.

	n	%	median	25%	75%
Age (years)			50.00	45.00	55.25
Type of surgery					
Mastectomy	14	36.8			
Lumpectomy	24	63.2			
Axillary lymph nodes dissection	35	92.1			
Radiotherapy	28	73.7			
Endocrine therapy	31	81.6			
Time since surgery (months)			34.00	20.75	60.50
Time since BCRL self-diagnosed (months)			24.00	8.75	45.00
Self-reported dominant arm					
Right	38	100.0			
Left	0	0			
Patients who had surgery on their self-reported dominant side	17	44.7			
Grip strength on dominant side			21.88	19.08	24.60
			mean 21.49 (SD = +/- 4.59)		
Grip strength on non-dominant side			20.23	17.79	23.55
			mean 20.4 (SD +/– 4.40)		
			dominant/non -dominant grip strength comparison p=0.243		
Grip strength on affected side			21.63	19.09	23.79
			mean 21.05 (SD = +/- 4.29)		
Grip strength on unaffected side			20.43	17.70	24.68
			mean 20.84 (SD = +/- 4.75) dominant/non -dominant grip strength comparison p=0.810		
Patients who had lower grip strength in reported dominant side compared with non-dominant side	12	31.6			
Patients who had lower grip strength on reported dominant side than estimated value	21	55.3			
Patients with weakness in affected side among the 21 patients who had surgery on the reported non-dominant side	6	28.6			
Patients with weakness in affected side among the 17 patients who had surgery on the reported dominant side	9	52.9			

We also compared our findings with a study on people who did not have lymphoedema (Chau et al, 1998), whose dominant arm had 6.6±9.2% higher grip strength (measured by the Jamar dynamometer) than the non-dominant arm.

Results

Table 1 shows the 38 participants' demographic and clinical characteristics. The median age was 50.5 (interquartile range (IQR) = 45–55.25). Of all the participants, 36.8% (n=14) had a mastectomy and 92.1% had axillary lymph nodes dissection. Seventeen patients (44.7%) had surgery on their self-reported dominant side. The median time period from when patients had noticed their BCRL was 24 months. All patients reported they were right-handed. The grip strength on the reported dominant arm was slightly higher than the other side but there was no significant difference (Z=-1.174; P=0.243). There was no significant difference between the grip strength on the affected arm and unaffected side (Z=-0.244; P=.810). The mean of dominant hand grip was 5.38% higher than non-dominant hand grip in these patients. Twelve patients (31.6%) had lower grip strength in their reported dominant side compared with the non-dominant side.

Fifteen (39.5%) of the patients were found to have grip strength weakness in their affected arm. Among the 21 patients who received surgery on their non-dominant side, 28.6% (n=6) had grip strength weakness in their affected side. Of the 17 patients who had surgery on their dominant side, 52.9% (n=9) had grip strength weakness on the dominant side.

Table 2 shows the comparison between the patients who had surgery on their dominant side and patients who had surgery on their non-dominant side. The L-Dex score was significantly higher in patients who had surgery on their non-dominant side (median = 4.392; IQR=-0.405–9.257) compared with patients who had surgery on their dominant side (median=-0.086, IQR=-4.358–4.716). This means the affected limb in patients who had surgery on their non-dominant side had more fluids than the affected side in patients who had surgery on their dominant side.

The median volume of the affected limb in patients who had surgery on their non-dominant side was 301ml (IQR=261–316) in the hand, 753.3ml (673.1–906.3) in the forearm, 1130.5ml (938.3–1404.2) in the upper arm, and 2206.4ml (1935.1–2700.05)

Table 2. Comparison between patients who have had surgery on their dominant side and non-dominant side.

	Patients who had a surgery on their dominant side (n=17)			Patients who had a surgery on their non-dominant side (n=21)				
	median	25%	75%	median	25%	75%	*Z*	*P*-value
L-Dex	-0.086	-4.358	4.716	4.392	-0.405	9.257	-2.158	0.031
Affected side								
Volume of hand (ml)	281.00	243.50	329.00	301.00	261.00	316.00	-0.617	0.547
Volume of forearm (ml)	750.80	667.60	913.80	753.30	673.10	906.30	-0.161	0.885
Volume of upper arm (ml)	1105.00	928.85	1307.75	1130.50	938.30	1404.20	-0.279	0.794
Volume of whole arm (ml)	2089.40	1845.80	2536.45	2206.40	1935.10	2700.05	-0.396	0.706
Induration at forearm	6.30	4.95	8.25	6.80	5.45	8.20	-0.558	0.586
Induration at upper arm	7.00	5.65	8.20	7.60	6.10	8.95	-0.822	0.420
Induration at breast	5.60	4.35	7.55	4.50	3.75	6.50	-1.601	0.112
Unaffected side								
Volume of hand (ml)	278.00	246.00	327.50	291.00	257.50	317.00	-0.411	0.690
Volume of forearm (ml)	687.60	615.65	841.85	766.50	706.75	905.15	-1.688	0.095
Volume of upper arm (ml)	1035.80	875.20	1300.60	1158.60	982.35	1391.60	-0.925	0.367
Volume of whole arm (ml)	2012.50	1755.50	2470.45	2186.80	1966.10	2602.55	-1.306	0.199
Induration at forearm	6.50	5.50	7.35	6.70	5.85	7.70	-0.764	0.454
Induration at upper arm	6.60	5.90	7.85	7.60	6.15	8.90	-1.205	0.234
Induration at breast	6.70	4.45	8.65	4.50	3.75	7.00	-1.733	0.84
Relative oedema volume (%)								
Hand	1.10	-1.95	4.05	0.90	-5.70	5.55	-0.029	0.983
Forearm	7.40	2.50	11.85	-3.80	-9.50	-0.20	-3.772	0.000
Upper arm	4.00	0.40	7.55	1.60	-5.20	4.40	-1.541	0.126
Whole arm	4.50	2.20	7.20	-1.00	-5.65	3.35	-2.877	0.003
Grip strength (Kg)								
Dominant side	22.90	18.73	25.90	21.85	19.17	24.40	-0.352	0.733
Non-dominant side	21.60	18.63	25.48	19.4	17.28	22.80	-1.380	0.172
Affected side	21.60	19.23	24.85	21.65	18.71	23.33	-0.484	0.637
Unaffected side	22.90	18.05	26.15	20.25	17.20	23.63	-1.160	0.256

in the whole arm. The median volume of the affected limb in patients who had surgery on their dominant side was 281ml (243.5–329) in the hand, 750.8ml (667.6–913.8) in the forearm, 1105ml (928.85–1307.75) in the upper arm, and 2089.4ml (1845.8–2536.45) in the whole arm.

Tissue induration between the patients who had surgery on their dominant side and the patients who had surgery on their non-dominant side showed no significant differences.

Between the patients who had surgery on their dominant side and who had surgery on their non-dominant side, relative oedema volume in the forearm (Z=-3.773, p=0.000) and the whole arm (Z=-2.877, p=0.003) showed significant differences.

There were no significant differences between the patients with grip strength weakness and without grip strength weakness in their affected side (*Table 3*). The relative oedema volume in the group that had grip weakness tended to be higher than non-weakness group, however, there was no significant difference.

Discussion

All patients reported that their dominant arm was the right but 31.6% had a stronger grip in their left hand. Of the patients who had surgery on their dominant side, the weakness of grip strength appeared in more than half. The lack of strength might be caused by the reduced use of the arm. The dominant grip strength was 5.38% higher than the non-dominant grip strength in the study group, which is lower than the 6.6% reported in people who do not have lymphoedema (Chau et al, 1998). Additionally, 55.3% showed grip weakness in the reported dominant arm even though the median period from surgery was nearly three years. This was higher than reported in a study by Lee et al (2015) that showed 36.3% had weakness in the affected arm. Although there were no significant differences between the affected and unaffected hand grip strength in our study, a previous study has reported that patients who had surgery on their dominant side had a significantly higher grip strength in

Table 3. Comparison between patients with a weakness and without a weakness on their affected side.

	Patients with weakness (n=15)			Patients with no weakness (n=23)				
	median	25%	75%	median	25%	75%	*Z*	*P*-value
L-Dex	4.995	-3.451	10.856	0.433	-2.082	5.232	-1.090	0.286
Affected side								
Volume of hand (ml)	282.00	241.00	324.00	297.00	253.00	311.00	-0329	0.751
Volume of forearm (ml)	749.60	703.30	947.20	813.10	641.10	887.50	-0.075	0.953
Volume of upper arm (ml)	1130.50	898.70	1335.30	1105.00	948.30	1473.10	-0.254	0.813
Volume of whole arm (ml)	2157.20	1856.10	2655.10	2215.50	1835.50	2593.20	-0.224	0.836
Induration at forearm	6.30	4.60	8.40	6.80	5.60	8.10	-0.807	0.429
Induration at upper arm	6.80	5.20	9.60	7.30	6.50	8.10	-0.687	0.501
Induration at breast	5.00	4.50	8.40	4.50	3.80	6.40	-1.195	0.238
Unaffected side								
Volume of hand (ml)	272.00	250.00	314.00	296.00	260.00	318.00	-0.852	0.403
Volume of forearm (ml)	705.20	651.30	830.70	766.50	680.70	906.00	-0.971	0.344
Volume of upper arm (ml)	1083.90	887.80	1282.00	1149.60	935.50	1490.20	-0.672	0.516
Volume of whole arm (ml)	2067.20	1829.20	2449.00	2186.80	1837.20	2689.80	-0.732	0.478
Induration at forearm	6.40	4.60	7.70	6.60	5.90	7.70	-0.329	0.751
Induration at upper arm	6.30	5.60	8.80	7.60	6.40	8.40	-0.897	0.378
Induration at breast	5.10	4.30	7.70	4.90	3.90	8.20	-0.015	0.994
Relative oedema volume (%)								
Hand	3.90	-4.10	6.30	0.40	-2.90	4.60	-0.986	0.332
Forearm	6.50	-1.60	12.10	-1.80	-8.60	5.80	-1.807	0.073
Upper arm	3.30	-0.70	8.10	1.60	-2.90	5.50	-0.986	0.332
Whole arm	4.20	-0.70	8.60	0.30	-3.70	6.10	-1.538	0.127
Grip strength (Kg)								
Dominant side	21.90	19.20	24.60	21.85	18.55	24.70	-0.03	0.982
Non-dominant side	20.95	19.15	23.70	20.15	17.55	23.50	-0.358	0.729
Affected side	20.90	18.90	23.15	21.65	19.15	24.70	-1.060	0.296
Unaffected side	22.70	19.45	25.60	20.15	16.40	24.20	-1.239	0.224

the affected side rather than those who had surgery on the non-dominant side (Hayes et al, 2005). These different results may be a consequence of the small sample in our study.

The L-Dex measurement was significantly higher in the patients who had surgery on their non-dominant side compared with the patients who had surgery on their dominant side. However, relative oedema volume, which is also commonly used as a parameter of BCRL, was significantly higher in the patients who had surgery on their dominant side than the patients who had surgery on their non-dominant side. These results can be seen as contradictory, however, we see these phenomena in clinical settings. Partial oedema in a limb can be missed by predetermined routine measurement of circumferences of the limb.

Grip strength was slightly higher in the patients who had surgery on their dominant side. It is more difficult to avoid using the dominant side in daily life. A previous study reported whether the side of operation, the dominant or non-dominant, influenced the volume differences between arms (Dylke et al, 2013). Using the affected limb maintained muscle mass and this can result in a higher REV in the patients who had surgery on their dominant side. Furthermore, using a skeletal muscle pump in daily life is essential for the drainage of the lymphatic fluid. Therefore, the higher L-Dex in the patients who had surgery on their non-dominant side can occur as a result of the muscles in the affected limb not being used therefore reducing the effectiveness of the lymphatic system.

It was expected that patients with weakness would have more fluid than patients with non-weakness and the median was actually higher in these patients. However, there was no significant difference in L-Dex. Further explorations with a larger number of patients is needed.

In addition, the self-reported dominant arm can be different from the true dominant arm, which has more muscle and volume. This was shown in a population unaffected by lymphoedena (Gebruers et al, 2007). Patients with BCRL might have higher reversal rates of true dominancy from muscle wasting and muscle

tone loss in the limb due to the side effects of cancer treatment and the resulting reduced mobility and limb use. Therefore, we need to assess the true dominancy before and after surgery, and take it into account for BCRL diagnosis, and not only rely on circumference or volume of the limb.

L-Dex uses arm dominance in its algorithm, as it might contain more extracellular fluid in the muscle, which holds 70% water, to determine extracellular/intracellular fluid ratio. The true dominant arm which has more muscle can be different from the patients' reported dominant arm in this population. Fear of using the affected arm is a predictive factor of weakened limb function (Lee et al, 2015) and patients might facilitate muscle wasting in the affected arm through its lack of use. Given that potential muscle mass/muscle tone loss, and a loss of potential extrinsic pumping forces for the lymphatics occurs, education to minimise the risk of lymphoedema must be reinforced by encouraging patients to use their affected arm rather than to avoid using it, or using it less than normal.

The skin induration in the affected breast was significantly high in patients with no weakness while relative oedema volume and L-Dex tended to be higher in the patients with weakness. It cannot be determined whether the BCRL was worse in the patients with weakness because oedema volume and L-Dex were high, or whether the BCRL was worse in the patients without weakness because the skin tissue induration was high at that time. We need to continue the discussion to find the formula or algorithm to assess true BCRL after determining the true dominant arm.

Education needs to be continuous, as a study has showed the significant decrease of grip strength two years after receiving exercise education (Bendz and Fagevik Olsen, 2002).

There are some limitations in this study. First, the sample size was small so there is a possibility of error. Therefore, further study with a large sample size is needed to support our hypothesis. Second, the exact muscle volumes/mass were not measured but grip strength was used as a surrogate measurement of muscle mass. To confirm whether a determination of the true dominant arm will affect L-Dex, accurate measurements of muscle mass by CT or ultrasound will be necessary in future studies.

The findings and the implications of the results give us reason to create a new strategy to estimate the true volume of any lymphoedema or of any pre-clinical lymphoedema. To determine the limb volume changes or ECF/ICF ratio as assessing BCRL, the true dominant arm rather than reported dominant arm should be considered.

Conclusion

Many patients with BCRL had grip strength weakness in their affected hand. 31.6% showed a reversal in the hand grip strength from their reported limb dominance. It is clear that patients' reported arm dominance can be different from the true dominant arm, which might have a greater muscle mass and thus larger volume. Determining and knowing the true dominant arm might affect the accuracy of the diagnosis of the true volume of lymphoedema and allow the earlier detection and the assessment of lymphoedema using L-Dex and circumference-determined volumes of the limb.

Assessments of true dominancy before and after treatment should be conducted at the same time as we assess for the early signs of BCRL or when it actually presents. Beyond this, the proper and continuous education regarding the importance of arm exercise to facilitate loading of the lymphatics and good lymph flow is needed for patients with breast cancer who might limit the use of their limbs due to a fear of developing or worsening BCRL.

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