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Difficulties with defining lymphoedema after axillary dissection for breast cancer

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Abstract:

Aim Axillary lymph node dissection(AND) is a common treatment for breast cancer. An important side effect of the surgery is lymphoedema (LO). The primary aims of this study were to assess the local prevalence of LO in patients who had undergone AND and how the subjective symptoms described by patients compare with objective measurements. Secondary aims were to investigate the relationship between risk factors and the prevalence of LO and to establish an easy and convenient way to detect LO patients in surgical clinics.

Method Eligible women after AND for breast cancer underwent three circumference measurements on the operated and non operated (control) arm. LO was defined as one or more measurements with an increase ≥7.5% than control after dominant arm correction. Questionnaires were used to assess severity of symptoms related to lymphoedema. 73 patients also had serial measurements in arms and change in arm volume in operated arm was calculated using Casley-Smith method and LO was defined as ≥20% increase in volume.

Results 193 women with AND were analysed. Mean age was 61 years and mean time since surgery was 56 months. The overall prevalence of LO was 23.3%. LO prevalence by arm volume was 8.2%. Using volume as the standard, an arm circumference increase of ≥7.5% and ≥10% showed a sensitivity and specificity of 83% and 81%, and 66% and 89% respectively. Significant risk factors for LO were age, radiotherapy and infection to the operated arm

Conclusion Circumference measures are a simple office method of screening for LO. A patient history and ≥10% increase in any circumference is optimal for determining LO after AND.

Assessment of axillary node status remains one of the single most important prognostic indicators in breast cancer, and may influence choice of adjuvant therapies. Until recently, Axillary Node Dissection (AND) has been the standard surgical technique to assess these nodes.

A serious side effect of AND is lymphoedema (LO). LO is a build up of lymphatic fluid in the arm caused by damage to arm lymphatic drainage when axillary lymph nodes are removed.[12] With moderate or severe lymphoedema, the affected arm can be painful, tired and heavy.[6,1,12,13] The excess lymphatic fluid acts as a culture medium and the disrupted lymph flow prevents a normal immune response making the arm[1] more susceptible to infection.

Patients are advised to take particular care of their affected limb and to seek medical treatment promptly if infection develops to try to minimise LO risk.[11] Long term LO is accompanied by subcutaneous and lymphatic fibrosis.[6]

The current literature around assessment of LO is confusing. There are several different measurement techniques in use, and consensus on definition of LO, particularly with arm circumference measures is poor. The incidence of LO is also changing over time as surgery and treatment techniques change. Due to these two factors the reported incidence ranges from 2–56%.[1]

This wide variation makes it difficult to compare studies and to know how a particular locality measures up to the published literature. It is important for both patients and surgeons to know the local risk for developing lymphoedema after AND. There is only one study to date in New Zealand to report local incidence of LO and it was retrospective study based on postal questionnaires.[20]

Several risk factors for developing LO have been previously determined, such as: treating the axilla with axillary radiation after AND, which causes tissue fibrosis, and chronic lymphoedema by constricting lymphatic channels.[12]

The primary aims of this study were to ascertain the local prevalence of lymphoedema after AND and to compare the relationship between the objective measures of LO and the subjective reporting of arm complications. Given the difficulty with LO definition, we decided to examine simple methods of assessment, in a subset, to determine which was best.

Secondary aims of the study were: to see if there were any local risk factors that affect the rate of LO; to measure the morbidity associated with LO using QoL questionnaire and to establish an easy and convenient way to detect LO patients in surgical clinic after AND

Methods

The participant population comprised consecutive women attending a breast cancer follow-up clinic at Waikato Hospital's Breast Care Centre or at a local surgeon's private rooms. Woman who met eligibility criteria were recruited when an interviewer was available.

Exclusion criteria included bilateral surgery; pre-existing lymphoedema prior to AND; less than 3 months after surgery; and surgery not carried out in the Waikato. Those who consented underwent an interview and arm assessment. The assessments were conducted by four trained staff members.

The assessment consisted of a questionnaire followed by an examination in which the patient's arm circumferences were measured. The questions were designed to find out risk factors for lymphoedema (arm work, post op breast/axillary wound infection or seroma collection, air flight travel, intravenous cannula to operated arm, arm infection or cellulitis and arm injury). Pathological and treatment details were obtained from medical records.

Quality of Life (QoL) questionnaire[16] included; activities requiring reaching overhead, driving car for > 15min, pulling shirt overhead, combing hair, doing up a back fastening bra, pushing a supermarket trolley with both hands, making a bed, zipping a back fastening dress, wiping down a table top, doing usual sporting activities (total of 10 questions and patients were asked to circle 0-4; 0=unknown, 1=no difficulty, 2=some problem, 3=very difficult, 4=unable to perform). Scores were summed for analysis.

Arm measurement was conducted using a tape measure. All of the participants had their arms measured 15cm above and 10 cm below the olecranon, and around the hand. The hand measurement was conducted by asking the participant to make a fist with the thumb on the outside of the fist, then measuring the circumference of the widest point, which is the base of the thumb and mid metacarpal.

To measure arm circumference for each point, minimal pressure with the tape was used to avoid compressing the arm soft tissues.

73 patients towards the end of study also had another 7 measurements starting from base of middle finger proximally every 10cm apart up to arm. A tape measure was used to mark points at 10cm intervals from middle finger on both hands with most distal point marked at 60cm from base of middle finger. Arm volumes were calculated using Casley-Smith method for calculation of volume of a truncated cone.[17]

Subjective questions were asked to ascertain which women had experienced ongoing problems with LO. They were asked to circle on a scale of 1–4 (1=no problems, 2=a little, 3=quite a bit and 4=very much), if since surgery they had experienced: arm swelling; heaviness; or tightness. For the purposes of analysis they were grouped as under: **Group 2+** that included those who circled 2, 3 or 4 for any of the questions; and **Group 3+** that circled 3 or 4 for any of the questions.

Statistical analysis—Data collected during interviews was then entered into a Microsoft Access database. We used multivariate logistic regression method for analysis of LO risk factors. A binary variable (lymphoedema Y/N) was the dependent variable. Statistical analysis for the Activities of daily living questionnaires was performed using GraphPad Prism (version 5.0). Continuous variables were compared using the Mann Whitney test. A p-value of <0.05 was retained as statistically significant.

Arm dominance correction—A correction was made for arm dominance using a factor of 1.4% for the forearm measurement, 1.2% for the hand measurement and 0% for the upper arm measurement. These figures were devised by using a subset of 105 women who said they had never had arm swelling and did not have any detectable swelling on measurement (at the 7.5% threshold). These women most probably do not have lymphoedema. The measurements of the dominant and non-dominant arms of these women were compared and the difference was found as detailed above.

These figures are comparable with those found in the literature. Kannus et al (1995) [14] found that the difference was 0.7% in the upper arm and 1.2% in the forearm. Another study [15] found the difference was 2.5%. Both of these studies had different population groups than the women in this study {healthy young controls} so the correcting factor determined in our own population was considered to be more accurate, and is what was used in the analysis.

Results

193 women with complete data were analysed. Patient demographics are shown in Table 1.

Table 1. Patient demographics

Variables	Mean ± SD
Age	61 ± 11 yrs
Weight	74 ± 17 kg
Height	157 ± 30 cm
BMI	28 ± 6 Kg/m^2
Time since surgery	56.42 ± 37.48 (3-183 months)

Lymphoedema in our study was defined as ≥7.5% increase in any circumference in the operated arm compared to non operated (control) arm after arm dominance correction. A 7.5% increase in circumference at all points is comparable to 15.5% increase in volume using formula:

$$\text{Area} = C^2/4\text{pi}.$$

A 7.5% increase at just one point, therefore indicates a much smaller increase in arm volume. A 10% increase in arm circumference corresponds to a 20% increase in arm

volume, if this occurs at all points and considerably less if just at one point. A ≥20% increase in arm volume is defined as moderate lymphoedema by an International Consensus Group.[19]

We also calculated the prevalence of LO using several different thresholds used in the literature (Table 2).

Table 2. Prevalence of lymphoedema using subjective and objective criteria

Criteria used to define lymphoedema	Percentage (number)
Subjective 2+ score (a little arm swelling or more)	41.9% (81)
Subjective 3+score (quite a bit of arm swelling or very much)	10.8% (21)
Any measurement ≥10% increase in operated arm	12.9% (25)
All 3 measurements ≥10% in the operated arm	0.0% (0)
Any measurement ≥7.5% increase in operated arm	23.3% (45)
All 3 measurements ≥7.5 in the operated arm	1.0% (2)
Any measurements ≥5% in the operated arm	40.9% (79)
All measurements ≥5% in the operated arm	2.1% (4)
Any measurement ≥2cm increase in operated arm	25.3% (49)
Volume ≥20% increase in operated arm	8.2% (6/73)
Volume ≥15% increase in operated arm	9.6% (7/73)
Volume ≥10% increase in operated arm	19.1% (14/73)

In a subset of 73 patients out of 193, serial measurements were done along with 3 basic measurements and we calculated % increase in volume in the operated arm compared to the other arm as control by using Casley-Smith method.[17] In this subset, the prevalence of LO was 8.2%, 9.6% and 19.1% using volume increase cut offs of 20%, 15% and 10% compared to non operated arm respectively.

International consensus guidelines for management of LO[19] define the LO in terms of volume increase as Mild < 20%, Moderate 20-40% and Severe >40% volume increase in operated arm. None of our women developed severe LO. Prevalence of LO using subjective method—i.e. subjective arm swelling at any time since surgery, was 10.8% (3+ score) and 41.9% (2+ score). Prevalence using ≥ 2cm increase in any circumference in operated arm was 25.3%.

We calculated the sensitivity and specificity of the circumference and subjective methods by comparing ≥20% increase in the volume as gold standard in the subgroup of 73 patients (Table 3).

Table 3. Sensitivity and Specificity of Subjective and Objective methods:

Different methods to detect lymphoedema	Sensitivity	Specificity
Any measurement ≥7.5% inc Op arm	83%	81%
Any measurement ≥10% inc Op arm	66%	89%
Any measurement ≥2cm inc Op arm	66%	80%
Subjective 3+ (quite a bit and very much)	67%	93%

Based on that, a 7.5% increase in circumference in the operated arm compared to the non operated arm has a high sensitivity to detect LO but still will call 19% of women with mild or no LO as having LO. Concordance between subjective and objective measurements is shown in Table 4.

Table 4. Concordance between the subjective and objective measurements

Variables	**Y/N**	**≥7.5% increase in any measurement (Total 45)** ***Number (Percentage)***
Arm swelling score 3+	NO	31 (69%)
(quite a bit and very much)	YES	14 (31%)
Arm swelling score 2+	NO	11 (24%)
(a little arm swelling or more)	YES	34 (75%)

Variables	**Y/N**	**≥10 % increase in any measurement (total 25)** ***Number (Percentage)***
Arm swelling score 3+	NO	13 (52%)
(quite a bit and very much)	YES	12 (48%)
Arm swelling score 2+	NO	2 (8%)
(a little arm swelling or more)	YES	23 (92%)

Variables	**Y/N**	**Arm swelling 2+**	**Arm swelling 3+**
≥7.5% increase in any measurement	NO	47	7
	YES	34(42%)	14 (67%)
	Total	81	21

Concordance using ≥7.5% increase in any circumference criteria was 31% in 3+ and 75% in 2+ groups. Of patients describing LO swelling; 67% of women with score 3+ (14/21) and 42% (34/81) with score 2+ group had LO on arm circumference measurements respectively. It shows that there is not good concordance between patients describing swelling at any stage since surgery and actual increase in arm circumference, when the ≥7.5% threshold is used. Using 10% threshold for LO; 48% had Subjective LO. It shows this threshold has more concordance with patient symptoms.

Risk factors for LO—Table 5 shows the risk factors analysis based on univariate analysis. Increasing age, infection to operated arm, LN positivity and radiotherapy to axilla/breast were significant risk factors. On multivariate logistic regression (Table 6), increasing age (p=0.02), radiotherapy to axilla (p=0.02), radiotherapy to breast (p=0.03) and infection to operated arm (p=0.02) were significant risk factors for development of LO.

Level of axillary dissection, lymph node positivity, chemo or endocrine therapy and operating surgeon (consultant vs registrar) had no significance for development of LO.

Table 5. Risk factors for lymphoedema (univariate)

Variables	Any measurement ≥ 7.5%	
TNM	T1	25.3%
	T2	21.6%
	T3	26.7%
Age	≤51	14.3%
	52–61	15.9%
	62–71	31.6%
	72+	34.4%
Infection or cellulitis to operated arm	No	21.6%
	Yes	62.5%
Radiotherapy	No	11.8%
	to Breast	25.4%
	to Axilla	50.0%
Chemotherapy	No	23.7%
	Yes	22.9%
Operating surgeon	Consultant	24.8%
	Registrar	19.2%
Positive nodes	≤0	23.6%
	1 to 3	16.7%
	4+	38.5%
Level of dissection	L2	21.3%
	L3	34.5%

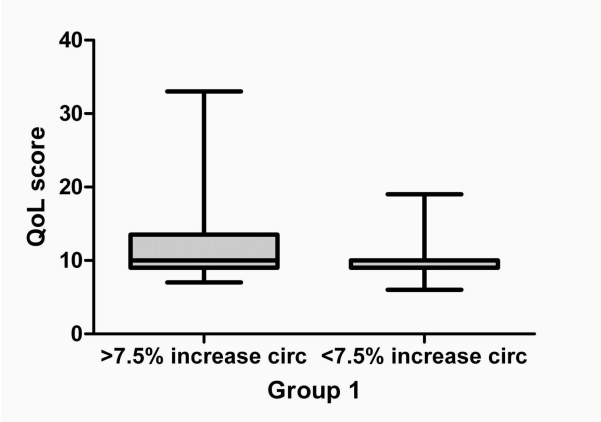
Table 6. Risk factors for lymphoedema (multivariate)

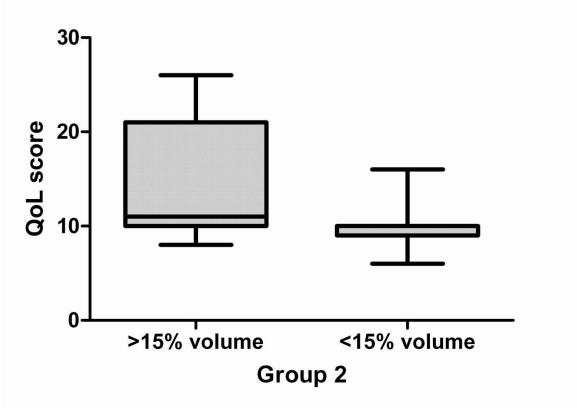
Variables	Odd ratio	P values
Age	1.1	0.02
BMI	1.1	0.08
Time since surgery	1.0	0.32
Operating surgeon	3.3	0.12
Level of axillary dissection	1.8	0.29
Lymph node positivity	1.0	0.49
Radiotherapy to breast	3.8	0.02
Radiotherapy to axilla	7.7	0.03
Chemotherapy	0.7	0.54
Endocrine therapy	2.1	0.14
Infection	6.7	0.02

Activities of daily living / QoL scores were summed and then the mean for the 193 women with arm circumferences compared using the ≥7.5% threshold and the 73 women with arm volume measures were compared using the 15% threshold. There was a significant increase in QoL scores in ≥15% volume increase group from mean of 9.9 to 14 with p-value <0.04. Mean scores were less significant in 7.5% increase in any circumference group(Table 7, Graph 1 & 2).

Table 7. Activities of daily living / QoL score

Variables	Mean ± SD	p-value
Any measurement ≥ 7.5% inc Op arm	12.5±5.7	<0.004
Any measurement < 7.5% inc Op arm	9.9±2.0	
Volume increase ≥ 15% Op arm	14±6.7	<0.04
Volume increase < 15% Op arm	9.9±1.6	





Discussion

There is a lack of international consensus on defining lymphoedema. This is due partly to different measurement techniques that are not directly correlated (including arm circumference measures, volume estimates from circumference, volume measurement by water displacement or infrared scanning and use of bioelectrical impedance).[2,8] In choosing a measurement technique, accuracy must be weighed up against ease of use.

In our study we used arm circumference measures as it is a quick procedure that can be done in the clinical setting with minimal expense on time or equipment. We adopted the protocol from IBCSG 10-93[16] which used 3 measurement sites for detection of LO. Volume measures by infrared or water displacement techniques are more accurate but require specialised equipment.

This study reports the rate of lymphoedema by several different criteria. This was done to enable comparison with other papers and to help determine the simplest and most accurate method of assessment.

Some women with lymphoedema only have swelling in one part of their arm and using a threshold increase at any single point enables detection of this. Using the percentage increase rather than an absolute measure {for example 2cm increase} takes into account the fact that to a large woman 2cm increase in the upper arm may be unnoticeable, but a smaller woman with a 2cm increase in circumference in the forearm or hand may have severe symptoms.

After choosing a measurement technique, the next step is choosing the threshold level at which a patient will be said to have lymphoedema. Listed below are some of the different definitions of lymphoedema found in a literature review using arm circumferences:

- ≥2cm difference in any circumference[4,8,6];
- ≥5% increase in circumference at any sites[(5- sensitivity 91%)]
- ≥10% increase in circumference at any site[(5- sensitivity 49%)]
- 5% difference in the sum of arm circumferences[2]
- >10% difference in the sum of arm circumferences[2]

The ≥2cm circumference yielded very similar results to the ≥7.5% increase in arm circumference group in our study, but in the subgroup with truncated arm volume measures, using a ≥2cm threshold was much less sensitive and specific. The ≥5% increase in circumference threshold for lymphoedema was too low in our study. It comes too close to the bounds of measurement error and gave a LO diagnosis rate of 41%. Using a ≥10% increase in circumference, our pick up rate was 12.9%. This threshold was also the most specific that we examined. The last 2 measures, lack adequate sensitivity.

Tewari et al[17] compared the volume displacement method with serial arm measurements and found out that there is a very high correlation ($p<0.0001$) between these two methods and recommended serial arm measurements for detection of LO. In our study we did serial measurements on 73 patients and found out that LO pick up rate using this technique was 9.6% and 19.1% using 15% and 10% increase in volume thresholds respectively. 15% threshold was used in SNAC trial group of RACS[18] and reported LO incidence of 6.9% in prospective manner which is comparable to our results. 10% increase in arm volume have been used by Bland KL et al.[5] to define LO.

International consensus for LO management[19] have defined LO based on percentage increase in volume as; Mild <20%, Moderate 20-40% and Severe >40% increase in arm volume. Based on this definition we had LO prevalence of 8.2%.

In our own data, a ≥7.5% increase in circumference at any site, appeared to be the most reasonable cutoff when the data were first examined, so this was used for the bulk of the analyses. However, of these women, 24% have never noticed any degree of arm swelling since surgery, and a further 45% have only had a little. Another common definition of mild lymphoedema is ≥2–5cm increase in arm circumference.

A cutoff of 7.5% falls right at the bottom of this range particularly for forearm, where LO was most commonly diagnosed. Using a definitions of LO from the SNAC Trial of ≥15% in arm volume, all three measures would have to increase by 7.5% (or some by much more than 7.5%) to meet the SNAC criteria—not just one. For an ≥20% for moderate LO from the International Consensus,[19] all three measures would have to increase by an average of 10%.

Only 2 women out of 193 had all 3 measures ≥7.5%. Using one measure increasing by ≥10% gets us closer to being consistent with these volume definitions, than the single measure ≥7.5%. Finally, using the ≥7.5% threshold, made very little difference in Activities of daily living / QoL mean score, from a numerical (i.e. practical perspective). On this basis, we considered the ≥7.5% threshold, is setting the cutoff too low, and not at an adequate level of specificity.

Many other studies used the pre-surgery volume of the arm as a control to be compared with later measurements. Our study instead used the opposite arm as a control. This is helpful in removing the effect of weight change over time (both arms should lose or gain weight equally), and to enable assessment when previous measures are not available. However it does raises the issue of handedness.

If the operated arm was the dominant arm, it is impossible to know if any difference is due to the lymphoedema or just the fact that the muscles of the dominant arm are larger due to greater use. Golshan and Smith[4] state that a >2cm circumferential difference is unlikely to be due to the dominant arm effect, and therefore any greater difference can be attributed to lymphoedema.

A strength of this study is that we have determined and used a correction factor for dominant arm based on measurements in subset of 105 women who said they never had arm swelling on subjective questionnaire and did not had any detectable swelling on measurement (at 7.5% threshold). This is an easy thing to do.

The subjective and objective measures showed poor concordance. This might be explained by the nature of the questions asked for subjective LO. Women were asked if they had experienced swelling of their arm at any time since surgery.

Some women may have had temporary swelling during the post-operative period, which was no longer there at time of assessment. Alternatively, some women may had LO successfully treated, so that minimal swelling was apparent at time of assessment. Our LO rate of 41.9% using subjective scores (2+, minimal symptoms), is comparable to the incidence of 38% reported in the Otago nursing study on lymphoedema published in 1997 based on subjective symptoms.[20]

Soren et al[7] assessed risk factors and how they affect the severity of lymphoedema. Soren study reported infection to operated arm, BMI and level of hand use to be significant risk factors for lymphoedema.

Our study had similar results for infection to operated arm as a significant risk factor for LO and we also found out that increasing age, radiotherapy to axilla or to the breast are also significant risk factor for LO. Increasing BMI showed a trend toward LO in our study on multivariate analysis and has been shown by others to be a significant factor.

Conclusions

- Measuring arm circumferences is easy and convenient office procedure to identify patients with LO and therapy can be started soon after with referral to LO specialist.
- Significant risk factors for LO are increasing age, infection or cellulitis to operated arm, radiotherapy to axilla and breast. These patients should be considered for more intensive LO screening so that referral and treatment may be started as early as possible.
- A 7.5 increase in any arm circumference above or below the elbow or at wrist was the most sensitive threshold to detect true cases of LO, but it lacks specificity and concordance with symptoms. We therefore recommend using a threshold of ≥10% increase in circumference at any site. This may readily be used for screening in clinic by clinicians and combined with subjective questions if clinician wish to improve sensitivity - the combination acting as a basis for referral to LO specialists.

Competing interests: None declared.

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