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Prevalence of lymphoedema more than five years after breast cancer treatment

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Abstract

Aim: A lack of consistency in the definition of breast cancer related lymphoedema (BCRL) and of uniform measurement criteria contribute to the wide prevalence range found in current literature. This report aims to describe the long-term prevalence of BCRL and secondly, to compare the long-term prevalence of BCRL when assessed by two objective measures and one subjective measure.
Methods: The upper-limbs of 145 post-surgical breast cancer patients were evaluated for the presence of lymphoedema using the water displacement method. Two circumference methods and patient perceived swelling were applied secondarily for comparison. Limb measurements were performed once, more than five years after surgery.
Results: The long-term prevalence of BCRL using water displacement was 8%. Prevalence varied when the sum of arm circumference (SOAC), the arm circumference and the self-report methods were used: 16, 31 and 17% [$P < 0.001$], respectively. Of the women identified with BCRL using the water displacement technique, 82% were detected with the SOAC method, 82% with the arm circumference method and 91% by self-report. Using water displacement as the gold standard the methods with the highest specificities were the SOAC (90%) and self-report method (89%), arm circumference resulted in a low specificity of 73%.
Conclusion: The prevalence of BCRL more than five years after surgical treatment differs depending on the measuring method used. Our data underlines the necessity for consensus on the diagnostic criteria for BCRL.

Keywords: Breast cancer related lymphoedema; Long-term prevalence; Water displacement; Circumference

Introduction

Early breast cancer detection and concomitant advancements in treatment options have not only resulted in an increase in breast cancer survival rates, but also in that of disease related morbidities with upper-limb lymphoedema being one of the most debilitating. Swelling of the oedematous limb is brought on by obstruction of normal lymph flow, with known treatment risk factors which cause damage to the lymph vessels being axillary dissection, mastectomy and adjuvant radiation therapy.[1–7] Breast cancer related lymphoedema (BCRL) could present with pain, loss of sensibility, strength and mobility of the affected limb, reducing activity and causing physical and psychological impairments.[8–12] Lack of consistency in the definition of BCRL and a lack of uniform measurement criteria have contributed to the wide prevalence range found in current literature.[1–4] This is illustrated in a review on the late morbidity after treatment of breast cancer, in which the prevalence was reported to range between 6 and 43%.[5] Moreover, few studies have described the long-term prevalence of BCRL[13–16] and none, to our knowledge, have done so with the use of different measuring methods within the same patient group.

Therefore, the current study was conducted primarily with the aim of assessing the long-term prevalence of BCRL in women more than five years after breast cancer treatment. We also sought to assess the source of variation in BCRL prevalence by comparing prevalence outcomes of four different measuring methods (water displacement method, two arm circumference methods and self-reported limb swelling).

Abbreviations: BCRL, breast cancer related lymphoedema; SOAC, sum of arm circumference; BIS, bioelectrical impedance spectroscopy.

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Patients and methods

Patients

A database of patients treated at the Maastricht University Medical Centre (MUMC+) between January 2001 and December 2003 was queried to identify women operated for breast cancer five or more years prior to search ($n = 386$). Exclusion criteria were death ($n = 96$), migration ($n = 8$) and loco-regional recurrence ($n = 34$). 248 eligible women were asked to take part in our study. 93 patients withheld written consent and ten patients ultimately did not take part due to personal circumstances or illness, resulting in a study population of 145 women. The hospital's medical ethics committee approved the study and the consent form.

Lymphoedema measurements

Four methods were used to assess the long-term prevalence of BCRL: the water displacement method, two arm circumference methods and the self-report method. The water displacement method was regarded as the gold standard. In order to evaluate the type of measurement as a probable source of variance, we compared the prevalence of the two circumference methods and the self-report method with the gold standard. All limb measurements were performed at one moment in time, five or more years after breast cancer surgery. For each method the breast cancer treated side was compared to the untreated side. One researcher (JS) performed all limb measurements.

Water displacement method

For the assessment of upper-limb volume a home built volumeter was used according to J. Lette.[17] This method carries a high reproducibility.[18] A line was drawn at 80% of the arm length, measured from the tip of the third digit to the tip of the acromion. Subjects were instructed to lower the arm straight and slowly into the volumeter and to stop and keep it still when the 80%-line reached the water surface. Both upper-limbs were measured twice. The overflowing water was collected in a bucket and weighed on a calibrated scale. (PR balance, Mettler-Toledo, Switzerland). The conversion value of 1 kg = 1000 mL was applied. Lymphoedema was defined as a limb volume difference greater than 200 mL between the treated and untreated side.

Circumference method

The arm circumference was measured at ten sites on both limbs using a tape measure. The locations measured were: mid-metacarpal, the wrist and at 20, 15, 10 and 5 cm below and above the elbow fold. The sum of these circumferences was calculated per limb. Lymphoedema was defined as a difference of the sum of arm circumferences (SOAC) of more than 5 cm between the treated and untreated side or as a difference of arm circumference of more than 2 cm between the treated and untreated side at any of the 10 measured locations on the limb.[19]

Self-reported lymphoedema

Patients were asked to indicate the presence of (refractory) swelling during a standardized interview by answering the following question with a "yes" or "no": Have you experienced swelling of the upper-limb on the breast cancer treated side in the past year? Self-assessment was described as negative or positive for BCRL.

Statistical analysis

Patient and clinical characteristics were described using descriptive statistics. Continuous variables were evaluated for normal distribution and expressed by providing the median and range. χ^2 was used to test the relationship between categorical variables. A P-value <0.05 was considered statistically significant. The sensitivity and specificity were measured for the SOAC, the circumference and the self-report methods, using the water displacement method as a reference. All data-analysis was conducted using SPSS for Windows 17.0 (SPSS Inc. Chicago, Illinois).

Results

Patient characteristics

The 145 women included in this study were evaluated for BCRL after a median period [range] of 6.2 years since time of surgery [5.0–7.8]. At time of surgery, subjects' age ranged from 33 to 86 years with a median of 55.0 years. The median [range] body mass index (BMI), calculated using the patients weight and height at time of surgery, was 25.1 [17.1–48.9]; a total of 28 patients were considered obese (BMI $\geq$ 30) at that time. The majority ($n = 123$) of the women underwent breast-conserving surgery; 22 women underwent ablative breast surgery. Of all patients, 69 had an axillary lymph node dissection (ALND) and 76 had a sentinel lymph node biopsy (SLNB). Radiation treatment either to the breast or chest wall and supraclavicular was given to 125 women.

Lymphoedema measurements

Using the gold standard, 11/145 women met the criteria of the water displacement method for the diagnosis of lymphoedema. When patients were evaluated for lymphoedema using the SOAC, the circumference and patient self-report methods, prevalence differed: 23/145, 45/145 and 25/145, respectively. The difference between the four prevalence rates was significant [$P < 0.001$]. Of the 28 obese women at baseline, 18 developed lymphoedema according to at least one of the four measuring methods [$P = 0.008$]. As for the 69 women who underwent ALND, almost half ($n = 37$) had either self-reported lymphoedema and/or

objectified limb swelling. In contrast, SLNB ($n = 24$) resulted in fewer patients with lymphoedema [$P = 0.007$].

Sensitivity and specificity of lymphoedema measurements

Table 1 presents the sensitivity and specificity of the SOAC, the circumference and self-report methods using the water displacement method as reference measure. The self-report method displayed the highest sensitivity of the three. Comparatively, the circumference and the SOAC methods each identified fewer women presenting with lymphoedema according to the water displacement method. The highest specificity was however measured by the SOAC method. Moreover, there were several cases in which patients had measured lymphoedema according to criteria of the SOAC ($n = 14$) or the circumference method ($n = 36$) without having a difference in limb volume greater then 200 mL and vice versa ($n = 3$).

Patient perception and measured lymphoedema

We were also interested in the prevalence of women with subjective lymphoedema. In order to get a wider scope on the problem at hand, we combined self-reported complaints of swelling with objective (measured) swelling. Table 2 presents patients categorized as follows: no BCRL (no subjective complaints and no measured swelling), asymptomatic BCRL (no subjective complaints but measured swelling), symptomatic non-BCRL (subjective complaints but no measured swelling) and symptomatic BCRL (subjective complaints and measured swelling). Once again, the prevalence rates varied depending on the diagnostic method used. Interestingly, there were women with the perception of arm swelling but without clinical signs of lymphoedema according to all three methods. However, there were also women with clinical signs of lymphoedema who did not have self-perceived arm swelling.

Discussion

Long-term prevalence

In the current study we assessed the prevalence of BCRL at a median time of 6.2 years after breast cancer surgery. To our knowledge this is the first study that used more than one measuring method for describing the long-term prevalence of BCRL. A wide point prevalence range of 8–31% was found in our data, with the circumference method at prevalence rate of 31% being the biggest outlier. In contrast, the water displacement, the SOAC and self-report methods yielded point prevalence estimates closer in range, 8–17%. Of the scant long-term data that is available, Sagen et al. reported a BCRL prevalence of 13% measured with the water displacement method five years after breast cancer treatment.[20]

Table 1
Sensitivity and Specificity. The sensitivity and specificity of the different methods are calculated using the water displacement method as reference measure, 95% confidence interval included. (Abbreviations: SOAC = sum of arm circumference, CI = confidence interval).

Measurement methods	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Circumference	82	0.48–0.97	73	0.65–0.80
SOAC	82	0.48–0.97	90	0.83–0.94
Self-report	91	0.57–0.99	89	0.82–0.93

Table 2
Patient perception and measured breast cancer related lymphoedema. Patients are divided into categories combining objective (measured) lymphoedema prevalence using the water displacement (gold standard), the SOAC or the arm circumference method with perceived swelling. (Abbreviations: BCRL = breast cancer related lymphoedema, SOAC = sum of arm circumference).

BCRL Category	Measurement methods		
	Water displacement	SOAC	Circumference
No BCRL (%)	82	76	63
Asymptomatic BCRL (%)	1	6	20
Symptomatic non-BCRL (%)	10	8	6
Symptomatic BCRL (%)	7	10	11

Lymphoedema: more than just limb swelling?

Lymphoedema constitutes more than just limb volume increase; symptoms that patients experience as result of that volume change should therefore also be identified. Creating BCRL sub-categories, depicting subjective complaints against the different objective measurements, resulted in a better insight on this topic.[21,22] Symptomatic BCRL was identified in 7% of the patients using the water displacement method; this was 10% for the arm circumference method and also 10% for the SOAC method. At a follow-up time of five years after breast cancer treatment McLaughlin et al reported a prevalence of 5% for symptomatic BCRL measured with the circumference method.[14] We assessed a point prevalence double that after a median time of 6.2 years, which is likely explained by the fact that our cohort included more women who underwent axillary lymph node dissection (47 vs. 36%).

Not all patients with self-reported complaints of BCRL had clinical measurable signs of limb swelling (symptomatic non-BCRL). The discordance seen between patient perceptions and measured swelling is consistent with the results reported in other studies.[14,23] A reason why not all of the subjective BCRL complaints might have shown a measured increase of limb volume or circumference could be due to the timing of the study. Many patients reported to have an increase in complaints after more than average exercise and with warm weather. The measurements in this study gave an impression of a patient's lymphoedema status at one specific moment in time, and thus, cannot exclude the existence of refractory limb swelling. Furthermore, symptomatic non-

BCRL could also be explained by sensory changes in the treated limb due to neurological damage caused by axillary surgery or radiation treatment. Vice versa, some women with measurable volume and or circumference difference had no subjective complaints of pain or swelling (asymptomatic BCRL). An important question is whether this BCRL category is clinically relevant; in other words if these patients will eventually go on to develop symptomatic BCRL.

Method selection: a matter for consideration

Volumetry is the most reliable method for the assessment of lymphoedema, with the classic water and the novel optoelectronic (perometer) volumeter forming the two methods of choice. Both methods have comparable reliability[24–27]; therefore, our selection of the water displacement method was based on cost-efficiency, the most applied method and readily available device. Even though we have used the water displacement method as our gold standard, we believe it to have its shortcomings in cases where minor swelling is accompanied by muscle atrophy. This can develop over time when normal use of the affected limb is avoided due to lymphoedema related symptoms, such as pain and heaviness. Minor volume increase in the form of extracellular lymph accumulation can be compensated by a volume decrease in muscle mass, in which case lymphoedema will go undetected. Bioelectrical impedance spectroscopy (BIS) on the other hand can accurately differentiate extracellular fluid from other tissues and thus solely assess lymph volume by measuring the impedance of a spectrum of low frequency electric current passed through a body region.[28–30] It could therefore be argued as to why BIS was not used in the current study as the gold standard for BCRL assessment instead of the water displacement method. Hayes et al described the short-term prevalence at six months after breast cancer treatment using the BIS method as the gold standard and the sum of arm circumference and the patient self-report method for comparison.[31] Importantly, in the early stages of lymphoedema swelling is refractory and predominately constitutes of extracellular lymph fluid, thereby making BIS a suitable tool for diagnosis.[32–35] However, as disease progression ensues, limb swelling becomes a more permanent entity with the occurrence of fibrosis and fat deposition.[36] As the aim of our study was to assess the long-term prevalence of BCRL five or more years after breast cancer treatment, some lymphoedema cases might have already progressed into the chronic phase during this period. Thus, the use of BIS instead of the water displacement method as the gold standard for the identification of BCRL in this study's setting is not justified. For lack of a more reliable assessment method we have accepted the possible limitations of the water displacement method.

Study limitation

A weakness of this study is the fact that it was performed without pre-operative or direct postoperative baseline measurements; these could have produced a more accurate identification of changes in limb volume and circumference. Instead, the contra-lateral upper-extremity was used as comparison to determine the presence of lymphoedema. Differences in circumference or arm volume may exist between a woman's dominant and non-dominant arm. In most women these differences are less than 2 cm and therefore not significant.[6,7] However, slight pre-operative limb volume or circumference differences might mask the presence of minor lymphoedema in the smaller extremity.

Conclusions

The prevalence of BCRL more than five years after surgical treatment differs depending on the measuring method used. The range of prevalence rates observed in this one group of women measured at a single point in time by four different methods, underlines the necessity for consensus on the diagnostic criteria for BCRL. Currently, there is no single measuring method that can identify lymphoedema error-free, this is in part due to the changing nature of lymphoedema. We advice screening breast cancer patients by using a combination of subjective complaints and pre-operative and sequential postoperative limb volume measurements (water displacement method), eliminating the chance of missing minor cases of limb swelling. This approach will result in more knowledge on the true prevalence of BCRL. Furthermore, the efficacy of therapeutic regimens and the design of optimal therapeutic approaches can be assessed creating the beginning of an accepted evidence based systemic approach of the problem of BCRL. Finally, the implementation of a lymphoedema screening program will clarify the clinical relevance of the asymptomatic BCRL and symptomatic non-BCRL categories.

Conflict of interest statement

The authors indicated no conflict of interest.

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