Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2011 April 1; 79(5): 1436–1443. doi:10.1016/j.ijrobp.2010.01.001.

A Standardized Method for Quantification of Developing Lymphedema in Patients Treated for Breast Cancer

Marek Ancukiewicz, PhD¹, Tara A Russell, BS, MPH¹, Jean Otoole, PT, MPH, CLT-LANA³, Michelle Specht, MD⁴, Marybeth Singer, MS, APRN-BC, AOCN, ACHPN⁵, Alexandra Kelada, BS¹, Colleen D. Murphy, MD², Jessica Pogachar, BS¹, Valeria Gioioso, BS¹, Megha Patel, BS¹, Melissa Skolny, BS, MPH¹, Barbara L Smith, MD, PhD⁴, and Alphonse G Taghian, MD, PhD¹

¹Department of Radiation Oncology, Massachusetts General Hospital

²Current Address: Division of Surgical Oncology, Brigham and Women's Hospital

³Department of Physical and Occupational Therapy, Massachusetts General Hospital

⁴Division of Surgical Oncology, Massachusetts General Hospital

⁵Division of Medical Oncology, Massachusetts General Hospital

Abstract

Purpose—The lack of standard method to quantify developing breast cancer related lymphedema (BCRL) impedes the progress in research and clinical practice. We therefore developed a simple and practical formula for quantifying both the asymmetry of upper extremities' volumes and their temporal changes.

Methods & Materials—We present the analysis of bilateral perometer measurements of the upper extremity in a series of 677 women who prospectively underwent lymphedema screening during their treatment for unilateral breast cancer at Massachusetts General Hospital between August 2005 and November 2008. Four sources of variation are analyzed: between repeated measurements on the same arm at the same session, between both arms at the baseline (pre-operative) visit, in follow-up measurements, and between patients. We analyze the effects of hand dominance, time since diagnosis and surgery, age, weight, and body mass index (BMI).

Results—The statistical distribution of variation of measurements suggests that the ratio of volume ratios is most appropriate for quantification of both asymmetry and temporal changes. Therefore, we present the formula for Relative Volume Change (RVC): $RVC = (A_2 U_1) / (U_2 A_1) - 1$, where A_1 , A_2 are arm volumes on the side of the treated breast at two different time points, and U_1 , U_2 are volumes on the contralateral side. RVC is not significantly associated with hand dominance, age, or time since diagnosis. Baseline weight correlates ($P=0.0016$) with higher RVC; however, baseline BMI or weight changes over time do not.

© 2010 Elsevier Inc. All rights reserved.

Corresponding author: Alphonse G. Taghian, MD, PhD, 100 Blossom Street, Boston, MA 02114, Tel: 617-726-6050, Fax: 617-726-3603, ataghian@partners.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflicts of Interest Notification:

Conflicts of interest do not exist

Conclusions—We propose the use of RVC formula to assess the presence and the course of BCRL in clinical practice and research.

Keywords

lymphedema; quantification; standardized method; perometer; breast cancer

INTRODUCTION

Early detection and treatment of breast cancer related lymphedema (BCRL) remains a challenge. Resulting as a complication of treatment, lymphedema is a swelling of the limb caused by an obstruction or alteration of lymphatic flow and is characterized by various microscopic and clinical changes. These changes may progress from reversible fluid accumulation, through pitting upon compression, and fibrosis, up to marked trophic changes as described in the staging classification of The International Society of Lymphology (1). Problems related to the presence of lymphedema include a feeling of heaviness and fatigue in the limb, decreased physical activity, and functional difficulties (2–6).

While diagnosis of BCRL is currently based largely on physical examination, various quantitative and objective methods of assessment have been studied and are being introduced into routine patient care (7–9). Among the quantitative measurements of BCRL, the most widespread is assessment of arm size, based upon either the measurement of circumference or direct measurement of volume. Other objective methods include measurements of lymph flow, tonometry (to evaluate compressibility) and bioimpedance (7,10–12).

We present an approach for BCRL assessment that employs perometry (13–15), a volume measurement technique that utilizes an array of moving optoelectronic infrared sensors (Figure 1). Perometry allows for fast, relatively accurate, and hygienic measurements of arm volumes and facilitates the routine monitoring of arm volumes in clinical practice. The reliability and accuracy of this method has been described previously (13–15).

Unilateral BCRL is characterized by an asymmetric increase of the volume of the arm affected by breast surgery and radiation. Monitoring the volume of the affected arm alone may lead to errors and potential misdiagnosis as volume changes can occur in both affected and unaffected arms due to changes in exercise behavior, hydration and weight gain or loss. Therefore, accurate assessment of lymphedema relies both on comparison to contralateral arm volume as well as earlier measurements of the same arm, usually prior to surgical intervention (16). The need to take into account both comparisons was argued persuasively by Armer (7) who noted that measurement of lymphedema by comparison with the other arm at only one time point is problematic, as it relies on an assumption of symmetry that is often false. Despite this suggestion, only few reported studies quantified lymphedema using both asymmetry and changes over time. Formulas that have been previously proposed, to address this goal, were not based on systematic study of measurement distributions and sometimes relied on unvalidated assumptions, for example that the volume of the unaffected arm does not change (17,18).

The lack of a standardized and reliable method of quantifying lymphedema has prevented establishment of a common definition of BCRL, has impeded comparison of different studies, and contributes to ongoing uncertainty regarding the epidemiology of BCRL, its clinical course, and response to treatment. Due to the lack of a standard definition, incidence of BCRL following surgery for breast cancer has been reported to vary between 0 and 56 % in various clinical studies (2).

In addition to the problems associated with definition and measurement of lymphedema, there is no consensus in the literature on how one should optimally express the volumetric changes. Should absolute (i.e., arithmetic differences) or relative changes (i.e., ratios) be used for the comparison of volumes between two arms, at different time points or for different patient groups? Most authors use the arithmetic difference between arm volumes or between earlier and subsequent measurements. However, appropriate quantification of the disparity between two sets of measurements depends on the underlying statistical distributions. Arithmetic difference between sample means is optimal with a normal distribution of measurements. Similarly, the ratio is optimal with log-normal distribution, because then logarithm-transformed measurements have a normal distribution and because the difference of two logarithms equals the logarithm of the ratio:

$$\log(a) - \log(b) = \log(a/b).$$

In this report, we analyze and discuss the statistical distribution of perometer measurements, separating variance components according to their different sources: as measurement variation in subsequent measurements performed on the same arm, as variation between left- and right-arm measurements performed at the same visit, as variation between patients, and as longitudinal variation over time. We model variance using a mixed model and analyze the effect of patient characteristics such as age, hand dominance, weight and BMI. We propose a method of accurate measurement and construct a simple formula for the quantitative assessment of developing lymphedema. The formula could be widely applicable for the evaluation of its clinical course and response to treatment.

MATERIAL AND METHODS

Patients and Data

Beginning August 2005, with approval of the Partners Institutional Review Board, we performed a prospective collection of bilateral arm volume measurements on breast cancer patients undergoing treatment at Massachusetts General Hospital. The perometer (Pero-System, Wuppertal, Germany) was used to measure both arm volumes pre-operatively (at baseline) and then post-operatively: before and after both chemotherapy and radiation therapy, and additionally at 3–7 months intervals following treatment completion. In this analysis, we utilize 10460 volume measurements performed on both arms during 2801 consecutive visits (i.e., we include all available data) of 677 consecutive patients, who had both pre-surgery (baseline) measurements performed between August 2005 and November 2008 and subsequent post-operative measurements. All these patients were treated surgically, 17% had surgery alone, 73% received radiation therapy, 42% received chemotherapy, 32% received all three treatment modalities. During each visit, between 1 and 3 measurements were performed on each arm. The clinical characteristics of the patient population are described in Table 1.

Perometer Measurement

All patients were measured by the Lymphedema Studies Clinical Research Coordinator. At a single sitting, patients were measured serially on the right and left arm, with up to 3 pairs (right and left) of measurements. Patients were positioned so that all measurements were taken from finger tip to axillary crease. The frame was moved at a slow and constant rate across the extremity. Throughout the course of this study, the measurement protocol was revised to increase accuracy of the measurements. Adjustments included: number of serial measurements, order of measurements (we initially performed serial measurements of right arm followed by serial measurements of left arm, then switched to a scheme where

measurements were performed in pairs: right and left arm, then right and left arm again, etc.), hand positioning, and angle of measurement.

Statistical methods

The analysis of measurement errors was performed using repeated measurements (2 or 3), performed on the same arm during a single visit. We calculate the “percent discrepancy”: the difference between larger and smaller of first two repeated measurements as a percentage of their mean and tabulate the percentage of patients with such discrepancies from 0–1%, 1–2%, 2–3%, 3–5%, and over 5%. Subsequent analyses were performed with the representative measurement defined as the median of these repeated measurements. First, the analysis of patient-to-patient variation was performed using measurements of both arms during the baseline (pre-operative) visit. The analysis of asymmetry between ipsilateral and contralateral arms was performed on baseline measurements, using volume differences and volume ratios. We also analyzed the statistical distribution of two measures of change (differences and ratios), between baseline and first post-surgery visit. We present the histograms and perform the Shapiro-Wilk test for normality (19).

Finally, the analysis of longitudinal variation was performed using post-surgery measurements in a mixed linear model (20), assuming auto-regressive correlation structure of serial measurements, where the fixed part of the model involved the ratio of ipsilateral to contralateral arm volumes at baseline, a B-spline function of time since surgery, time since diagnosis, patient weight (alternatively, body mass index), weight change, dominant hand, and age. The random part of the model included patient-specific intercept and logarithm of time since surgery. We used logarithmic transformation for asymmetry measure, time since diagnosis, and weight. Missing longitudinal weight measurements were replaced by the averaged weights of adjacent time points, otherwise the analysis was performed on patients with complete data. F-tests were performed for fixed effects covariates, and likelihood ratio tests for random-effects covariates.

RESULTS

Between May 2005 and November 2008, N=677 consecutive women diagnosed with unilateral breast cancer were evaluated with the perometer at both pre-operative (considered here as baseline) and post-operative visit(s). Table 1 shows the demographic and clinical characteristics of the patient population.

We performed a total of 5224 volume measurements of each arm, during 2798 patient visits. In order to evaluate the reliability of arm volume assessment, repeated measurements (2 or 3) of the same arm at the same sitting were taken during 2123 visits (76%). During each visit, all volumes were calculated using constant length of arm utilized for perometer measurements. Repeated measurements of both arms were obtained at baseline in 498 patients (74%). The variation of repeated baseline measurements was evaluated using the percent discrepancy as defined above. Figure 2A shows the histogram of percent discrepancy of baseline measurements of the right arm, while Table 2 lists the fractions of patients with percent discrepancy in intervals: 0–1%, 1–2%, 2–3%, 3–5%, and more than 5% for right-arm, left-arm, and for the ratio of right to left arm volumes.

We defined the representative perometer measurement as the median of two or three repeated measurements (for $n=2$, median by definition, equals mean) and analyzed the variation of these representative measurements between patients, between arms and over time. Figure 2B displays the histogram of representative ipsilateral-side arm volume measurement at baseline; these data exhibit substantial between-patient heterogeneity and left-skewed distribution. The statistical distribution of these measurements is log-normal

rather than normal: the Shapiro-Wilk test rejected the hypothesis of normal distribution of volumes of both arms (both P-values $<10^{-10}$), and did not reject the hypothesis of log-normal distribution ($P=0.18$ for the tumor-side arm and $P=0.34$ for the opposite arm). As expected for baseline measurements, there was no statistically significant difference between representative measurements of tumor-ipsilateral and contralateral arms ($P=0.42$, paired Wilcoxon test).

Next we investigated the statistical distribution of different measures of disparity between baseline volumes of ipsilateral-side arm (A) and contralateral-side arm (U): the difference A-U, the ratio A/U, and the log-transformed ratio A/U. The hypothesis of normal distribution was rejected for all 3 cases, with P-values, respectively $<10^{-10}$, $<10^{-6}$, and $<10^{-4}$ (Shapiro-Wilk test). The skewness coefficients were, respectively, 0.45, 0.53, and 0.34, showing that out of these disparity measures, log-transformed ratio A/U most closely approximated the normal distribution. Although baseline A/U might be expected near 1 for almost all patients, the ratio exhibited a remarkable variation, with 10-th and 90-th percentiles 0.954 and 1.053, respectively; and with 11.2% of patients having A/U in excess of 1.05.

In the next step, we examined the statistical distribution of various measures of change between baseline and a follow-up visit. Our interest was here primarily in the variation of normal cases, so we used the first post-surgery visit (on average, 56 days following surgery) where relatively few patients might have yet developed lymphedema. We compared the following measures of change between baseline and post-surgery A/U ratios: the arithmetic difference of these ratios ($A_1/U_1 - A_0/U_0$), ratio of ratios ($(A_1/U_1)/(A_0/U_0)$), and log-transformed ratio of ratios ($\log(A_1/U_1)/(A_0/U_0)$). The hypothesis of normal distribution was rejected by Shapiro-Wilk test for the first two instances with P-values, respectively, 0.031 and 0.003, but not so for the log-transformed ratio of ratios ($P=0.078$, Shapiro-Wilk test), which points to log-normal distribution of the ratio of A/U ratios over time.

Our data are comprised of baseline, post-surgery, and follow-up measurements. Three or more serial measurements were available in 566 (84%) of patients, four or more in 394 (58%) patients, five or more in 232 (34%), six or more measurements in 134 (20%) patients. In order to evaluate the effect of covariates on longitudinal variation of RVC we performed the analysis using mixed effects model among 228 patients who had 5 or more measurements and complete data (4 patients with missing data were excluded).

In the analysis of longitudinal variation of RVC (Table 3), patient weight was the only covariate significantly associated with expected value of RVC ($P=0.0016$, F-test), among the following covariates: time elapsed since surgery, age, weight, weight change since baseline, dominant use of the ipsilateral arm, and time from diagnosis to baseline evaluation. Patients with higher baseline weight tended to develop higher RVC in follow-up, however the effect was small as the doubling of a patient's body weight was only associated with increase of RVC by 2.2% (95% confidence interval from 0.9% to 3.4%). A similar analysis with body mass index in place of patient weight did not show any significant correlation of body mass index with RVC (data not shown). Time since surgery was not associated with expected RVC, however, it was a highly significant factor affecting patient-to-patient variation of follow-up RVC ($P<0.0001$, likelihood ratio test). Therefore mean RVC did not increase significantly in a population as a whole, but patient-to-patient variation changed over time, a fact which likely reflects the time course of developing lymphedema in a subset of patients.

Finally, we analyzed the effect of longitudinal variation in arm length measurement on perometer calculations. There was slight variation in the length of arm measured from visit to visit for most cases, however volumes were always calculated using constant arm length

during the visit. The effect of arm length on the expected value of RVC was not statistically significant ($P=0.4659$, F-test) using mixed effects model as described above with the inclusion of arm length as a covariate.

For the sake of better accuracy and consistency in measurement, we furthermore propose a measurement protocol which reflects the result of this analysis and our experience with the perometer (Figure 3).

DISCUSSION

Our study proposes a practical and straightforward measure of unilateral BCRL based on serial assessment of arm volume asymmetry. We used perometry to measure upper extremity volumes and our data confirm the reliability of this technique (11,13,14). The statistical distribution of measurement errors was skewed with occasional large errors. The combined effect of measurement errors in both arms, evaluated as percent discrepancy of right-to-left volume ratios, exceeded 3% and 5% for 7.4% and 1% of patients, respectively. During evaluation of serial arm volume changes, the measurement errors reflect errors made at baseline and follow-up; a simple mathematical calculation shows that the magnitude of such errors increases by a factor $\sqrt{2} \approx 1.41$ with respect to measurement errors at one time point. Our data indicate that the discrepancies of serial changes in right/left volume ratios would exceed 3% for 17% of patients, and exceed 5% for 5.8% of patients. Therefore, caution should be taken in interpreting perometry results if only a single measurement of each arm is obtained.

We were able to substantially reduce this error by obtaining two measurements of each arm at each time point. If the two measurements are in agreement, with less than 1% difference, the mean of these two measurements is used. If the difference is greater than 1%, a third measurement is obtained and the median value is used. This effectively eliminates large occasional errors: if the probability of an error exceeding 5% is 0.01 in a single measurement, the probability of 2 such errors in 2 trials is 0.0001 (the chances are still lower that the erroneous measurements will agree within 1%), and the probability of 2 erroneous measurements exceeding 5% in 3 trials is <0.0003 .

The asymmetry between volumes of ipsilateral arm (A) and contralateral arm (U) can be calculated as either the difference $A-U$ or the ratio A/U . The statistical distribution of the difference $A-U$ is non-normal and strongly skewed; furthermore these differences cannot be subject to log-transformation as they might be zero or negative. On the other hand, we found that the statistical distribution of A/U at baseline approximates a log-normal distribution, and that the distribution of ratios of A/U over time is also log-normal. These findings suggest that a better measure of the asymmetry between arms is the ratio rather than difference and those ratios of such ratios should be used for comparison between different time points. Consequently, we propose that the following formula for Relative Volume Change (RVC), which takes into account both asymmetry between arms and temporal changes:

$$RVC=(A_2/U_2)/(A_1/U_1) - 1,$$

where A_1 , A_2 are arm volumes on the side of treated breast at baseline and during follow-up, and U_1 , U_2 are arm volumes on the opposite (untreated) side; a unit is subtracted from the result in order to get a more intuitive interpretation where no change corresponds to zero rather than one. Our formula for RVC can be thought of as a simple approximation to log-transformed ratio of ratios (21), a measure found to have a normal distribution.

Our RVC formula accounts for baseline asymmetry between arms. Based on our data, baseline asymmetry can be substantial: baseline A/U were below 0.954 for 10% of patients and exceeded 1.053 for another 10% of patients; for 11.2% of patients the baseline volume of ipsilateral arm exceeded the volume of contralateral arm by 5% or more. Accounting for baseline asymmetry is particularly important when monitoring for mild lymphedema, as the lack of such adjustment might seriously diminish the specificity of the diagnosis.

Using RVC, we studied the longitudinal relationship with time since surgery, and patient-specific factors: baseline A/U ratio, age, baseline weight, body mass index, weight changes over time, time since diagnosis, dominant arm, as well variation in arm length used for perometer measurements. Time since surgery was not significant for prediction of expected value of RVC but correlated strongly with extent of patient-to-patient variation ($P < 0.0001$) (a likely cause of this phenomenon is development of lymphedema in a small subset of patients). The patient baseline weight had a statistically significant effect on RVC, but interestingly body mass index, or changes of patient weight over time, did not have such an effect. The length of arm evaluated during a perometer measurement was not correlated with RVC, therefore if this parameter is kept constant during a single perometry session, its effects on the volume of each arm cancel each other in RVC, consequently arm length does not necessarily need to be standardized and kept constant over follow-up time.

Although our study used perometer measurements, the RVC equation could also be evaluated for other techniques based on bilateral measurements of arm sizes, for example, arm circumference, or water displacement. With repeated measurements of the same arm, a similar principle can be employed to select a representative measurement; furthermore the variation between arms, between patients, and variation over time does not depend on instrumental errors of a particular technique. For the sake of comparability, the RVC formula should be always used to quantify volume changes. That is, when circumference measurements are utilized, they should not be used in place of volumes, but rather the volume of each arm needs to be calculated (we suggest using the standard frustum formula (22)), then RVC formula applied to the calculated volumes.

In conclusion, there is no standard quantitative index available for reporting serial assessment of lymphedema. Therefore, it is difficult to describe epidemiology, clinical course, and treatment of lymphedema, to compare different studies, and apply the results of clinical research to clinical practice. We propose the use of our protocol and formula for quantification of relative volume change, $RVC, (A_2U_1)/(U_2A_1)-1$, for standardized reporting of volumetric monitoring of lymphedema both in clinical practice and research.

Acknowledgments

Research Support: The project was supported by Award Number R01CA139118 (AGT) and Award Number P50CA089393 (AGT) from the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. This study was also partially supported by the Tim Levy funds for Breast Cancer Research, the Jane Mailloux and the Blanche Montesi funds.

REFERENCES

1. The diagnosis and treatment of peripheral lymphedema. Consensus document of the International Society of Lymphology. *Lymphology*. 2003; 36:84–91. [PubMed: 12926833]
2. Erickson VS, Pearson ML, Ganz PA, et al. Arm edema in breast cancer patients. *J Natl Cancer Inst*. 2001; 93:96–111. [PubMed: 11208879]
3. Clark BSJ, Harlow W. Incidence and Risk of Arm Oedema Following Treatment for Breast Cancer: A Three-Year Follow-up Study. *Q J Med*. 2005; 98:343–348.

4. Hayes SC, Janda M, Cornish B, et al. Lymphedema after breast cancer: incidence, risk factors, and effect on upper body function. *J Clin Oncol*. 2008; 26:3536–3542. [PubMed: 18640935]
5. Paskett ED, Naughton MJ, McCoy TP, et al. The epidemiology of arm and hand swelling in premenopausal breast cancer survivors. *Cancer Epidemiol Biomarkers Prev*. 2007; 16:775–782. [PubMed: 17416770]
6. Ridner SH. The psycho-social impact of lymphedema. *Lymphat Res Biol*. 2009; 7:109–112. [PubMed: 19534633]
7. Armer JM. The problem of post-breast cancer lymphedema: impact and measurement issues. *Cancer Invest*. 2005; 23:76–83. [PubMed: 15779870]
8. Armer JM, Stewart BR. A comparison of four diagnostic criteria for lymphedema in a post-breast cancer population. *Lymphat Res Biol*. 2005; 3:208–217. [PubMed: 16379589]
9. Ridner SH, McMahon E, Dietrich MS, et al. Home-based lymphedema treatment in patients with cancer-related lymphedema or noncancer-related lymphedema. *Oncol Nurs Forum*. 2008; 35:671–680. [PubMed: 18591171]
10. Gerber LH. A review of measures of lymphedema. *Cancer*. 1998; 83:2803–2804. [PubMed: 9874401]
11. Warren AG, Janz BA, Slavin SA, et al. The use of bioimpedance analysis to evaluate lymphedema. *Ann Plast Surg*. 2007; 58:541–543. [PubMed: 17452840]
12. Ridner SH, Montgomery LD, Hepworth JT, et al. Comparison of upper limb volume measurement techniques and arm symptoms between healthy volunteers and individuals with known lymphedema. *Lymphology*. 2007; 40:35–46. [PubMed: 17539463]
13. Stanton AW, Northfield JW, Holroyd B, et al. Validation of an optoelectronic limb volumeter (Perometer). *Lymphology*. 1997; 30:77–97. [PubMed: 9215977]
14. Petlund, C. *Volumetry of Limbs*. Boston: Olszewski & Waldeman; 1991. *Lymph Stasis: Pathophysiology, Diagnosis and Treatment*; p. 443–451.
15. Tierney S, Aslam M, Rennie K, et al. Infrared optoelectronic volumetry, the ideal way to measure limb volume. *Eur J Vasc Endovasc Surg*. 1996; 12:412–417. [PubMed: 8980428]
16. Stout Gergich NL, Pfalzer LA, McGarvey C, et al. Preoperative assessment enables the early diagnosis and successful treatment of lymphedema. *Cancer*. 2008; 112:2809–2819. [PubMed: 18428212]
17. Boris M, Weindorf S, Lasinski B, et al. Lymphedema reduction by noninvasive complex lymphedema therapy. *Oncology (Williston Park)*. 1994; 8:95–106. discussion 109–110. [PubMed: 7993730]
18. Brown J. A clinically useful method for evaluating lymphedema. *Clin J Oncol Nurs*. 2004; 8:35–38. [PubMed: 14983761]
19. Conover, W. *Practical non parametric statistics*. 3rd ed.. New York: John Wiley & Sons; 1999.
20. Demidenko, E. *Mixed Models: Theory and Applications*. John Wiley & Sons; 2005.
21. Abramovitz, M.; Stegum, I., editors. *Handbook of mathematical functions with formuals, graphs and mathematical tables*. Dover; 1970.
22. Sander AP, Hajer NM, Hemenway K, et al. Upper-extremity volume measurements in women with lymphedema: a comparison of measurements obtained via water displacement with geometrically determined volume. *Phys Ther*. 2002; 82:1201–1212. [PubMed: 12444879]

Figure 1. The Perometer
A: The Perometer Device
B: Perometer Volumetric Output
C. Perometer Image Output

Figure 2. Histograms showing different sources of variation

A: Percent discrepancy of first two measurements of the right arm at baseline

B: Volume of ipsilateral side arm (A) at baseline

C: Ratio of arm volumes on ipsilateral and contralateral sides at baseline (A/U)

D: Ratio of A/U ratios at the first post-surgery visit and baseline

Log-scale used for histograms B-D.

Figure 3. Perometer Protocol and Appropriate Positioning

Table 1

Demographic and clinical characteristics of the patient population

Breast diagnosed with tumor	
Right	321/677 (47.4%)
Left	356/677 (52.6%)
Age at diagnosis *	56 [48,64] (N=677)
Female gender	677/677 (100%)
BMI (kg/m ²) at baseline	26.5 [23.4,30.6] (N=550)
Weight (kg) at baseline	69.3 [61.7,79.8] (N=565)
Height (cm) at baseline	161 [158,166] (N=637)
Days from diagnosis to evaluation	16 [12,22] (N=677)
Dominant use of hand	
Left	70/652 (10.8%)
Right	579/652 (88.8%)
Both	3/652 (0.5%)
Node biopsy	
ALND	164/675 (24.3%)
SLNB	407/675 (60.3%)
No axillary surgery	104/675 (15.4%)

* For age and other continuous variables, the table shows medians with first and third quartiles and the number of patients analyzed

Percentages of patients with a certain magnitude of percent discrepancy (D) for two repeated baseline measurements.

Table 2

Percent discrepancy	0 – 1%	1 – 2%	2 – 3%	3 – 5%	>5%
R: Right arm volume	60.2%	25.1%	8.0%	6.0%	0.6%
L: Left arm volume	80.1%	16.5%	2.6%	0.6%	0.2%
R/L: Ratio of right / left arm vol.	51.6%	29.9%	10.0%	7.4%	1.0%
$\sqrt{2} \times R/L$: Change of R/L ratio *	42.2%	25.5%	15.3%	11.2%	5.8%

* The last row presents the percentage of patients with discrepancies of the ratio of right to left (R/L) volumes magnified by $\sqrt{2} \approx 1.41$ (as expected in assessment of R/L change over 2 time-points).

Table 3

P-values for fixed-effect covariates (F-test) and random-effect covariates (likelihood-ratio tests) in the mixed effects model of longitudinal variation of *RVC*

Covariate		RVC
		P-value
Fixed effects	Intercept	0.0070
	Baseline A/U	0.1077
	B-spline function of time since surgery	0.5830
	Age at baseline	0.9957
	Baseline weight	0.0074
	Weight change since baseline	0.2603
	Dominant ipsilateral arm	0.8565
	Time from diagnosis to baseline	0.8831
Random effects	Intercept	
	Time since surgery	<.0001