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ORIGINAL RESEARCH

Early Contralateral Shoulder-Arm Morbidity in Breast Cancer Patients Enrolled in a Randomized Trial of Post-Surgery Radiation Therapy

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Abstract

Introduction: Shoulder/arm morbidity is a common complication of breast cancer surgery and radiotherapy (RT), but little is known about acute contralateral morbidity.

Methods: Patients were 118 women enrolled in a RT trial. Arm volume and shoulder mobility were assessed before and 1–3 months after RT. Correlations and linear regression were used to analyze changes affecting ipsilateral and contralateral arms, and changes affecting relative interlimb differences (RID).

Results: Changes affecting one limb correlated with changes affecting the other limb. Arm volume between the two limbs correlated ($R = 0.57$). Risk factors were weight increase and axillary dissection. Contralateral and ipsilateral loss of abduction strongly correlated ($R = 0.78$). Changes of combined RID exceeding 10% affected the ipsilateral limb in 25% of patients, and the contralateral limb in 18%. Aromatase inhibitor therapy was significantly associated with contralateral loss of abduction.

Conclusions: High incidence of early contralateral arm morbidity warrants further investigations.

Keywords: early breast cancer, short-course radiation therapy, image-guided radiation therapy, shoulder/arm morbidity, breast cancer-related lymphedema

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Introduction

Breast cancer is the most common cancer in women worldwide with highest incidence rates recorded in northern and western Europe, in Australia and in North America.[1] In the United States, it has been estimated that 2,632,005 women of all ages were alive with an ever diagnosis of invasive breast cancer.[2] Survivors bear the risk of treatment sequels that can affect daily life activity.[3–5] Lymphedema of the arm is a swelling of the arm resulting from an increase in interstitial fluid due to a failure of lymph drainage.[6] The pathogenesis is variously explained by surgery and/or radiotherapy damage to collecting lymphatics, disturbance of protein concentrations and hemodynamic factors.[6,7] The incidence of lymphedema has varied widely from 0%–3% to 58%–65%, depending on the breast cancer treatment, patient related risk factors, the length of follow-up, and the methods used to measure and to define lymphedema.[5] Known risk factors are the extent of breast and axillary surgery, radiation treatment (RT), and obesity.[5,7–10] Impaired shoulder mobility might result from axillary and chest wall fibrosis, from neural damage or lymphedema, or from damage to vasculature or to the musculoskeletal system.[7] Risk factors appear comparable to lymphedema, and reports on the incidence of shoulder mobility impairment have also varied widely from 0.8% to 67%.[3] This suggests that lymphedema and impaired shoulder mobility might occur conjointly,[11] therefore a systematic evaluation on how measurements of arm volume relate to measurements of shoulder mobility appears warranted. It might also be noted that in the evaluation of breast cancer treatment outcomes on shoulder-arm morbidity, changes in volume of the arm and changes in mobility of the shoulder on the operated side typically have been assessed in comparison with the contralateral limb.[3–5] No study have investigated contralateral shoulder-arm morbidity on its own, except in one report of early arm swelling affecting both sides after breast surgery.[12] Since assessment of shoulder-arm morbidity, occurring after therapy, relies on measures of the contralateral limb as reference,[13] contralateral arm swelling or loss of mobility could have an important impact on the detection of morbidity.

In the present study, our aim is to explore the early 2-months post-RT onset of arm swelling and loss of shoulder mobility in patients who were enrolled in a clinical trial of post surgery radiotherapy for breast cancer, taking the opportunity that arm volume and shoulder mobility were prospectively recorded in the enrolled patients. Specifically, the study will look (1) at correlations between changes of arm volume and changes in shoulder mobility measurements within the same limb, (2) at correlations between the ipsilateral and the contralateral limb, and (3) an explorative analysis will be done to evaluate factors affecting the risk of arm swelling and shoulder mobility impairment.

Materials and Methods

Selection of patients

The study population were women who gave informed consent to participate in the UZ-Brussel ethics board approved TomoBreast clinical trial (ClinicalTrials.gov registration NCT00459628). The trial opened on May 1, 2007 and closed on August 31, 2011. Eligible patients were women aged 18 years or older, presenting with a primary breast carcinoma, completely resected by total mastectomy or by tumorectomy, stage pT1-3 N0M0 or pT1-2 N1M0 with pathological nodal status assessed by sentinel nodes biopsy or by axillary lymph node dissection, who were to receive post-surgery RT. Women who gave written informed consent were allocated to either a control group or to an experimental group by computer randomization balanced by nodal status, type of surgery, and chemotherapy sequence using Efron's biased coin design. Planned total accrual was 118 patients based on a power of 0.80 to detect a 5% vs. 25% incidence of all heart and lung toxicities between the two treatment arms (primary endpoint, not the purpose of the present study).

In the control group, a dose of 50 Gy was delivered in 25 fractions over 5 weeks by conventional RT to the chest wall using tangential photon fields, and to the supraclavicular, infraclavicular and axillary nodes in case of pN1status, using an anterior field matched to the tangential fields. Breast conserved patients received an additional boost of 16 Gy in 8 fractions over 2 weeks to the initial tumor bed using a direct electron field.

In the experimental group, a dose of 42 Gy was delivered in 15 fractions over 3 weeks by short-course IGRT (image guided RT) to the chest wall in case of total mastectomy or the whole breast in case of tumorectomy, and to the supraclavicular, infraclavicular and axillary nodes in case of pN1status. Breast conserved patients received a simultaneous integrated boost of 9 Gy delivered during the same 15 fractions.

Surgery quality assurance was testified through accreditation of the UZ Brussel's Breast Clinic as a recognized reference center ("Gespecialiseerd oncologisch zorgprogramma borstkanker", Federal Public Service, www.health.belgium.be). Radiotherapy procedures for the conventional group have been previously reported by Voordeckers et al.[14,15] Procedures and specifications for contouring of organs at risk and target volumes for the IGRT group have been reported by Reynders et al.[16] TomoBreast physics implementation were supervised by TR, all treatment plannings underwent full RT staff review for approval prior to delivery, radiation treatment procedures were supervised by the RT department's quality officer (MR).

Physical therapy assesment

Assessments by a physical therapist were done before RT (baseline evaluation) and at 2 ± 1 month after RT (first follow-up). Further assessments were planned yearly up to 3 years after RT, these are on-going. The volume of the arms were obtained from circumference measurements using the mean of the frustum and the cylinder model methods.[17–19] Measurements that were recorded for the evaluation of shoulder mobility were:[20–28] (1) *Anteflexion*, the maximum range of active forward elevation of the arm, in degrees; (2) *Retroflexion*, the maximum range of active backward elevation of the arm, in degrees; (3) *Abduction*, the maximum range of active lateral elevation of the arm, in degrees; (4) *Endorotation*, measured by counting the vertebrae between C7 and the most cranial vertebra the patient could reach with her thumb on her back; (5) *Scapular distance*, measured in cm as the distance between the spine and the angulus inferior of the scapulae, with the arms in 90° anteflexion. Note that signs of shoulder-arm mobility impairment are indicated by *decreased* values of abduction, retroflexion, and anteflexion, and by *increased* values of endorotation and scapular distance.

For each type of measure obtained in a patient, volume, anteflexion, retroflexion, abduction, endorotation, and scapular distance, we derived the patient's corresponding relative interlimb difference (RID), expressed as the percent difference between ipsilateral and contralateral arm. The RIDs were computed as: *RID* = 100 * (*ipsilateral measure* − *contralateral measure*)/*contralateral measure*. That is, for volume, the *RID* was computed as 100 * *(ipsilateral arm volume − contralateral arm volume)/(contralateral arm volume)*.[29] For anteflexion, the *RID* was computed as 100 * *(ipsilateral arm anteflexion − contralateral arm anteflexion)/(contralateral arm anteflexion)*, and so on for retroflexion, abduction, endorotation, and scapular distance.

Patients' subjective arm symptoms were scored during the physical therapy assessment. A score of 1 was attributed when any of the following subjective symptoms was present in the ipsilateral arm/hand: altered sensations, heaviness, swelling, fatigue, warmth, burning, pain, or when actions required more effort. A score of 0 indicated no subjective symptoms.[24,25,30–33] Other data recorded at physical therapy assessment were patient's age, operated side, dominant side, weight and height, type of breast/axillary surgery, time interval between assessments, hormone therapy, aromatase inhibitor therapy, RT to locoregional lymph nodes and chemotherapy.

Statistical analysis

The outcomes of interest were the changes over time that occurred between baseline (pre-RT) and at the first follow-up (post-RT). We use the notation "Δ" to designate the change over time, computed as the value of a measure made at follow-up, minus the value of that measure made at baseline. That is, in a patient having at baseline ipsilateral arm volume of 1802 mL and contralateral arm volume of 1677 mL, and, at follow-up, ipsilateral arm volume of 1908 mL and contralateral arm volume of 1657 mL, we compute the three following Δ changes:

1. Ipsilateral Δ volume = +106 mL (=1908–1802 mL).
2. Contralateral Δ volume = −20 mL (=1657–1677 mL).
3. Δ volume RID = volume RID at follow-up–volume RID at baseline = +7.6% (=15.1%–7.5%),

where, by applying the RID definition,

15.1% = 100 * (1908−1657)/1657 is the volume RID at follow-up,

and

7.5% = 100 * (1802−1677)/1677 is the volume RID at baseline.

Descriptive analysis used histograms distributions of the Δ RIDs. Grading of limb edema used the Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0), with grade 1 representing 5%–10% interlimb discrepancy, grade 2 > 10%–30%, and grade 3 > 30%.[13] For grading of mobility impairment, CTCAE did not define a lower bound to take into account common intra-individual asymmetry. In absentia, a Δ RID lower bound of 10% or more was used as indicator of mobility impairment.[34] Paired Student t-tests were used to evaluate the univariate statistical significance of the changes. Multivariate correlations were used in order to examine the relationships between the changes affecting arm volume and the changes affecting measures of shoulder mobility, and between the ipsilateral and the contralateral side for absolute measures. Ordinary least squares regression were used to explore factors that could affect the changes in arm volume and shoulder mobility. All Δ changes were analyzed as continuous response variables. Independent variables considered for inclusion in regression models were patients' age (continuous), patient's shoulder-arm symptom score (binary), body mass index (BMI, continuous), weight change after RT (continuous), time interval between assessments (continuous), type of breast surgery (mastectomy vs breast conserving, coded as binary), axillary surgery (dissection vs. sentinel node biopsy, coded as binary), side of surgery is side of dominant arm or not (binary yes vs. no), chemotherapy (binary yes vs. no), hormone therapy (binary yes vs. no), aromatase inhibitor therapy (binary yes vs. no), type of RT (binary short-course IGRT vs. conventional), RT to lymph node areas (binary yes vs. no). In order to select among the models, we used the Bayesian information criteria (BIC).[35] BIC penalizes models which use a large number of parameters and penalizes for sample size. Variables were selected only if they improve the model's information according to the BIC. Considering that response variables were not independent (multiple dependent outcomes), we further penalized the selected models by adjusting their *P*-values using the false discovery rate controlling procedure of Benjamini and Yekutieli.[36]

General statistical computations and regression analyses used JMP v. 9.0.2 (SAS Institute, Cary NC, USA). Computation of adjusted *P*-values used function "p.adjust" from R version 2.14.1.[37]

Results

Between May 1, 2007 and August 31, 2011, 123 women consented to participate, of whom 2 were ineligible (1 bilateral breast surgery, 1 retracted consent). Of the 121 eligible, 62 were assigned to conventional RT, 59 to short-course IGRT. For the present study, two patients had no follow-up physical therapy assessment, and one patient with a baseline weight of 150 kg was excluded, on consideration of that extreme outlying value relative to other patients' weight range which was 42–102 kg, leaving 118 patients evaluable for analyses. One patient had a contralateral arm paralysis since childhood, the scapular distance and arm mobility could not be measured and were assigned as missing values. One patient was confined to a wheelchair at pre-RT assessment, retroflexion was not measurable and was assigned as missing value. Two patients had pre-RT measurements of retroflexion exceeding 90°, the corresponding records could not be checked, these were also assigned as missing values.

Follow-up cutoff date was October 14, 2011. Median times of physical therapy assessment were 38 days (interquartile range IQR 31-45) from surgery to first physical therapy (baseline) assessment, 6 days (IQR 3-9) from baseline to start of RT, and 105 days (IQR 93-121) between baseline and the first post-RT follow-up. Table 1 summarizes the patients' characteristics. The age distribution of the patients enrolled in the trial tended to be younger than patients treated in the institution,[38] reflecting that older patients were reluctant to accept randomization. Nevertheless, patients older than 70 years represented a substantial 12.7% of patients recruited. Regarding body mass index, half of the study population were overweight. Arm symptoms were present prior to RT in 18.6%. Half of the patients received breast conserving surgery with sentinel nodes biopsy only.

Distribution of the Δ RIDs showed for volume that 28% (=33/118) of the patients had a Δ volume RID exceeding 5% (CTCAE grade 1 limb edema). Excess Δ volume RID was on the ipsilateral limb (positive Δ volume RID) in 19 (=58% of 33) patients, on the contralateral limb in the other 14 (=42% of 33) patients (negative Δ volume RID indicating a relative volume increase of the contralateral limb). By CTCAE grade 2 or more limb edema, Δ volume RID exceeding 10% was observed on the ipsilateral limb in 5% (=6/118) and on the contralateral limb in 3% (=3/118) of the patients (Fig. 1, top left histogram). Regarding mobility, Δ RID exceeded 10% on the ipsilateral limb by abduction in 21% (=25/117), retroflexion in

Table 1. Patients' characteristics.

	N 118	% 100
Age (median 54, interquartile range IQR 48–67)		
<50 years	33	28.0
50–60 years	45	38.1
61–70 years	25	21.2
>70 years	15	12.7
Weight pre-RT (median 65.5, IQR 58.7–75.8)		
<70 kg	70	59.3
≥70 kg	48	40.7
Body mass index (median 24.9, IQR 22.4–28.8)		
<25 kg/m^2	60	50.8
≥25 kg/m^2	58	49.2
Arm symptoms pre-RT		
Unknown	11	9.3
No	85	72.0
Yes	22	18.6
Chemotherapy		
No	64	54.2
Yes	54	45.8
Hormone therapy		
No	18	15.3
Yes	100	84.7
Aromatase inhibitor		
No	69	58.5
Yes	49	41.5
Type of surgery		
Breast conserving + sentinel nodes biopsy	59	50.0
Mastectomy + sentinel nodes biopsy	13	11.0
Breast conserving + axillary dissection	17	14.4
Mastectomy + axillary dissection	29	24.6
Operated side is dominant		
Unknown	1	0.8
No	62	52.5
Yes	55	46.6
Type of radiotherapy (randomization arm)		
Conventional	61	51.7
Short-course IGRT	57	48.3

22% (=25/114), by anteflexion in 17% (=20/117), by endorotation in 23% (=28/114), and by scapular distance in 17% (=20/117) of the patients. Δ RID exceeded 10% on the contralateral limb by abduction in 15% (=18/117), retroflexion in 25% (=29/114), by anteflexion in 3% (=4/117), by endorotation in 31% (=35/114), and by scapular distance in 21% (=24/117) of the patients (Fig. 1, other histograms). Considering combined Δ RIDs exceeding 10%, 25% (=29/118) of the patients had at least one of volume or abduction impairment of the ipsilateral limb, and 18% (=21/118) had at least a volume or abduction impairment of the contralateral limb.

Comparisons of the means of pre- and post-RT measurements found no significant changes between baseline and 2-months follow-up, other than a significant mean weight increase of 0.8 kg and a contralateral arm loss of abduction of 6 degrees (Table 2). Notably, none of the arm volume assessments either by absolute measure or by relative difference showed a significant change.

Multivariate correlations among the different measurements and between ipsilateral and contralateral arms are displayed in Table 3. The corresponding graphical display is shown in Figures 2–4. In order to interpret the correlations, we need to recall the conventions that we used: morbidity is indicated by *increases* of measurements regarding arm volume, endorotation, and scapular distance, whereas morbidity is indicated by *decreases* of measurements of abduction, retroflexion, and anteflexion. Hence, the significant correlations indicated concordant impairments within the ipsilateral arm (ipsilateral vs. ipsilateral, upper left quarter of Table 3): increase of arm volume correlated with loss of abduction (correlation coefficient R = –0.32) and impairment of scapular movement (R = 0.19). Likewise, concordant impairments were noted between abduction, anteflexion, and endorotation. Retroflexion however showed no significant correlation. Within the contralateral arm (contralateral vs. contralateral, lower right quarter of Table 3), a similar relationship was noted between arm volume and abduction (R = –0.24), and between arm volume and scapular distance (R = 0.32). Impairment of abduction significantly correlated with anteflexion, endorotation, and scapular distance in the same limb. No significant correlation was found for the contralateral retroflexion.

Comparison of ipsilateral vs. contralateral arm shows that changes affecting one limb strongly correlated with changes affecting the other limb (upper right quarter of Table 3). The highest correlations were abduction (R = 0.78), retroflexion (R = 0.73), scapular distance (R = 0.65), and arm volume (R = 0.57), all P-values <0.001. Other correlations also indicated concordant impairments. The only discordant exception that we found was the –0.16 coefficient between ipsilateral retroflexion and contralateral abduction.

Results of the exploratory analyses according to the type of response outcome are summarized in Table 4.

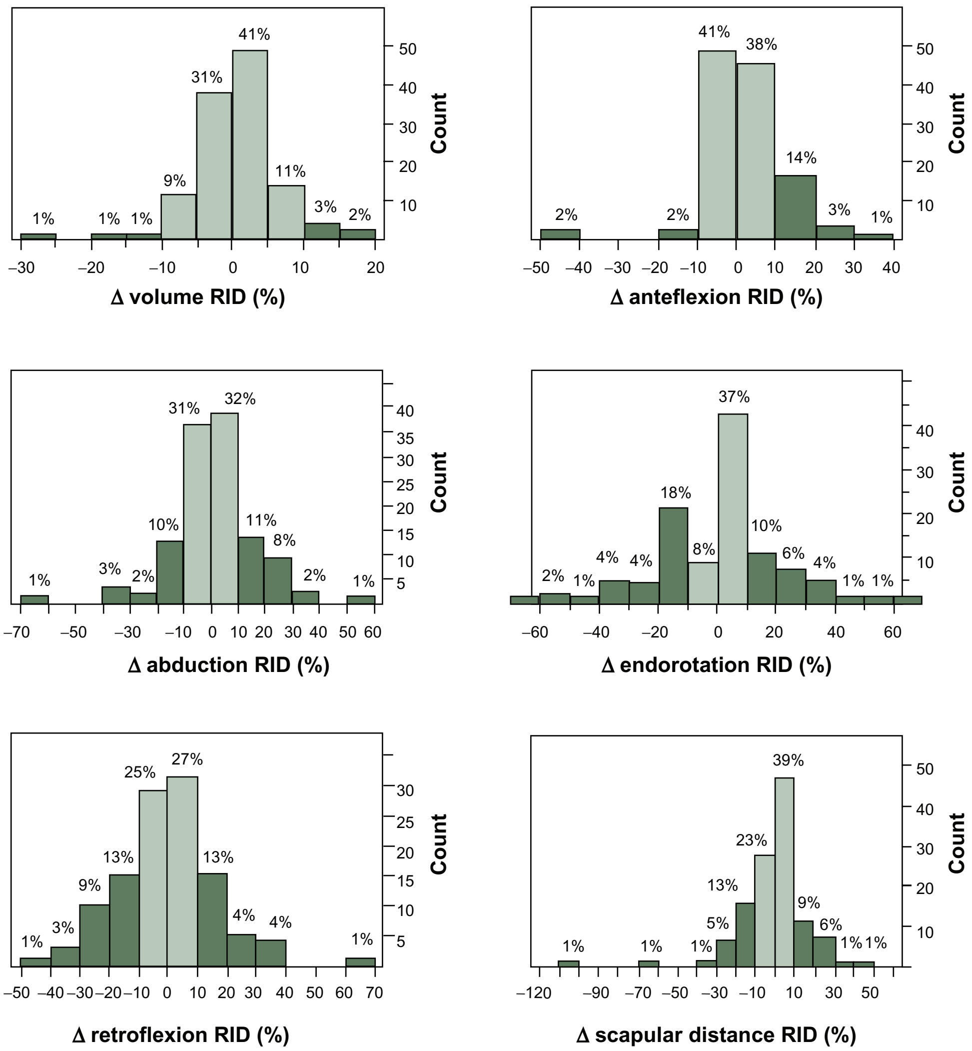

Figure 1. Distributions of the pre- to post-radiotherapy changes (Δ) of the relative interlimb differences (RID).

By RIDs, only the presence of pre-RT arm symptoms was identified as a significant factor. The sign of the coefficient for the presence of pre-RT arm symptoms indicated that pre-RT arm symptoms were associated with improved ipsilateral abduction and anteflexion, relatively to the contralateral arm.

By absolute assessments, increased body weight and axillary lymph node dissection were positively associated with change of arm volume, ipsilaterally as well as contralaterally. Axillary lymph node dissection was associated with impairment of ipsilateral and contralateral scapular movement. Radiotherapy to regional nodes was associated with impaired ipsilateral abduction, while aromatase inhibitor therapy was associated with impaired contralateral abduction. The presence of pre-RT arm symptoms was associated with improved ipsilateral abduction, anteflexion, and endorotation. We also note an association between mastectomy and improvement of ipsilateral anteflexion and contralateral scapular distance.

Discussion

A priori, there is no reason why the contralateral limb should be considered as being at risk of morbidity. Our attention was drawn following an interim analysis of the TomoBreast trial which was done to ascertain against unexpected toxicities.[39] The circumstances of patients for whom physical therapy assessment was difficult raised the question to which extent contralateral limb morbidity could confound measurements.

In a consecutive series of 193 women undergoing unilateral breast cancer surgery who were assessed for arm volume before surgery and at 6 weeks post-surgery, Haines and Sinnamon observed a 10% or greater

Table 2. Arm and shoulder changes from pre to post-radiotherapy.

Mode of evaluation	Side	Measurement	Pre-RT	Post-RT	Mean change Δ	Standard error of Δ	*P*-value
Absolute	No laterality	Weight (kg)	67.5	68.3	0.8	0.4	0.034
	Ipsilateral	Arm volume (mL)	1654.5	1670.2	15.7	10.8	0.148
		Abduction (°)	121.7	118.7	–3.0	2.6	0.254
		Retroflexion (°)	48.8	47.4	–1.3	0.9	0.150
		Anteflexion (°)	140.7	142.9	2.3	1.4	0.111
		Endorotation (n)	7.2	7.1	–0.2	0.2	0.291
		Scapular distance (cm)	13.7	14	0.3	0.2	0.159
	Contralateral	Arm volume (mL)	1640.1	1645.3	5.2	9.7	0.591
		Abduction (°)	129.0	123.0	–6.0	2.6	0.023
		Retroflexion (°)	49.1	47.8	–1.3	1.0	0.202
		Anteflexion (°)	148.5	148.7	0.2	1.1	0.879
		Endorotation (n)	7.0	6.8	–0.2	0.1	0.152
		Scapular distance (cm)	13.8	14.1	0.4	0.2	0.097
Relative	Percent difference ipsilateral vs. contralateral	% volume diff	0.7	1.3	0.6	0.6	0.282
		% abduction diff	–4.5	–3.0	1.5	1.4	0.274
		% retroflexion diff	0.1	–0.3	–0.4	1.6	0.790
		% anteflexion diff	–4.5	–2.9	1.5	1.0	0.119
		% endorotation diff	8.2	8.4	0.3	2.7	0.921
		% scapular distance diff	0.2	–0.9	–1.1	1.6	0.503

absolute volume increase in one or more segments of the upper limbs, ipsilaterally in 35% of the patients, and contralaterally in 32% of the patients.[12] Our finding that an almost equal number of patients experienced contralateral grade 1 limb edema, 14 of 118 patients, as compared with ipsilateral edema in 19 of 118 patients, closely matches that report. Haines and Sinnamon reported correlations of the volume changes between ipsilateral and contralateral arms ranging from 0.38–0.44 between distal segments, to 0.55–0.64 between proximal segments. We found a remarkable concordant correlation of 0.57 between the ipsilateral and the contralateral volume changes (Table 3). Correlations of volume changes between the two limbs are also suggested in a prospective study of 196 patients assessed preoperatively and at 3-months intervals postoperatively.[40] With an average time to onset of 6.9 months, 43 women developed lymphedema. Among unaffected patients, volume of the contralateral limb showed no change between baseline and follow-up, from 1253 mL to 1252 mL, whereas among affected patients, volume of the contralateral limb increased from 1315 mL to 1341 mL, as compared with the ipsilateral limb which increased from 1331 mL to 1377 mL.[40]

Our regression analysis indicated that weight gain and axillary lymph node dissection contributed to increase of arm volume on both sides (Table 4). It is understandable that weight gain might affect both limbs. However it is unclear why dissection on one side should affect the contralateral limb. Redistribution of lymph flow from the ipsilateral to the contralateral side has been hypothesized.[12] Such redistribution have been shown to occur in a lymphoscintigraphic study of radiotracer distribution, before surgery-radiotherapy and 6 months thereafter.[41] In 20 patients in whom uptake of activity could be demonstrated prior to surgery-radiotherapy, only one patient revealed drainage to the contralateral axilla. After treatment, lymphoscintigraphic cross over to the contralateral axilla was found in 6 out of 11 patients. Chemotherapy might have been a contributing factor, either directly by favoring capillary leakage,[42] or indirectly by the use of subcutaneous infusion ports which have been known to increase the risk of thrombosis.[43] However, chemotherapy was not significant in our regression analysis.

The contralateral arm was also affected by loss of mobility, with a loss of contralateral abduction as measured by Δ RID exceeding 10% in 18 of 117 patients, as compared with ipsilateral loss of abduction in 25 of 117 patients. Similarly to arm volume, contralateral and ipsilateral loss of abduction were highly correlated, R = 0.78 (Table 3). We found no directly comparable evidence from the literature to support our

Table 3. Ipsilateral and contralateral correlations (95% confidence intervals) of shoulder-arm Δ changes.

Side	Ipsilateral				
	Abduction	**Retroflexion**	**Anteflexion**	**Endorotation**	**Scapular distance**
Ipsilateral					
Arm volume	**–0.32***** (–0.48, –0.14)	–0.01 (–0.19, 0.18)	–0.1 (–0.28, 0.09)	0.1 (–0.09, 0.28)	**0.19*** (0.00, 0.36)
Abduction		–0.04 (–0.22, 0.15)	**0.38***** (0.20, 0.52)	**–0.20*** (–0.37, –0.01)	–0.09 (–0.27, 0.10)
Retroflexion			0.13 (–0.06, 0.31)	–0.08 (–0.26, 0.11)	–0.14 (–0.32, 0.05)
Anteflexion				–**0.31***** (–0.47, –0.14)	**0.19*** (0.01, 0.37)
Endorotation					0.09 (–0.10, 0.27)
Scapular distance					
Contralateral					
Arm volume					
Abduction					
Retroflexion					
Anteflexion					
Endorotation					

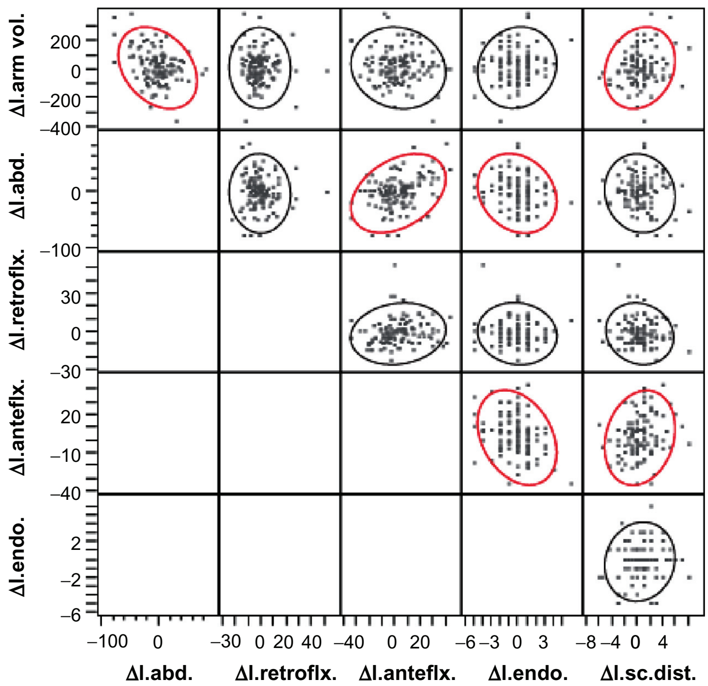

Figure 2. Correlations among ipsilateral shoulder-arm changes.
Notes: Δl. = changes observed on the ipsilateral limb after breast radiotherapy, for measurements of abduction (abd.), retroflexion (retroflx.), anteflexion (anteflx.), endorotation (endo.), scapular distance (sc.dist.), and volume (vol.). Ellipses: 95% confidence density. Red colored ellipses indicate statistically significant correlations ($P \leq 0.05$).

Contralateral					
Arm volume	**Abduction**	**Retroflexion**	**Anteflexion**	**Endorotation**	**Scapular distance**
0.57*** (0.43, 0.68)	**–0.32***** (–0.48, –0.14)	0.05 (–0.14, 0.23)	–0.08 (–0.26, 0.11)	0.01 (–0.18, 0.19)	**0.35***** (0.17, 0.50)
–0.21* (–0.38, –0.02)	**0.78***** (0.70, 0.85)	–0.02 (–0.20, 0.17)	**0.26**** (0.08, 0.43)	**–0.18*** (–0.36, 0.00)	**–0.17*** (–0.34, 0.02)
–0.02 (–0.20, 0.17)	**–0.16*** (–0.33, 0.03)	**0.73***** (0.63, 0.81)	–0.03 (–0.22, 0.15)	–0.04 (–0.23, 0.14)	–0.14 (–0.32, 0.05)
0.04 (–0.15, 0.22)	0.09 (–0.09, 0.27)	–0.03 (–0.21, 0.16)	**0.41***** (0.24, 0.55)	0 (–0.19, 0.18)	0.09 (–0.10, 0.27)
–0.02 (–0.20, 0.17)	–0.09 (–0.27, 0.10)	–0.07 (–0.25, 0.12)	0.09 (–0.10, 0.27)	**0.46***** (0.30, 0.60)	**0.18*** (–0.01, 0.35)
0.16* (–0.02, 0.34)	**–0.18*** (–0.36, 0.00)	–0.11 (–0.29, 0.07)	0.02 (–0.16, 0.21)	**0.16*** (–0.02, 0.34)	**0.65***** (0.53, 0.75)
	–0.24** (–0.41, –0.06)	0.01 (–0.17, 0.2)	–0.11 (–0.29, 0.08)	0 (–0.19, 0.18)	**0.32***** (0.14, 0.48)
		–0.06 (–0.24, 0.13)	**0.32***** (0.14, 0.48)	**–0.28***** (–0.45, –0.1)	**–0.24**** (–0.4, –0.05)
			0.05 (–0.14, 0.23)	–0.1 (–0.28, 0.08)	–0.01 (–0.19, 0.18)
				–0.11 (–0.29, 0.08)	0.03 (–0.16, 0.21)
					0.09 (–0.1, 0.27)

Notes: *$P = 0.01$ to 0.05; **$P = 0.001$ to <0.01; ***$P < 0.001$.

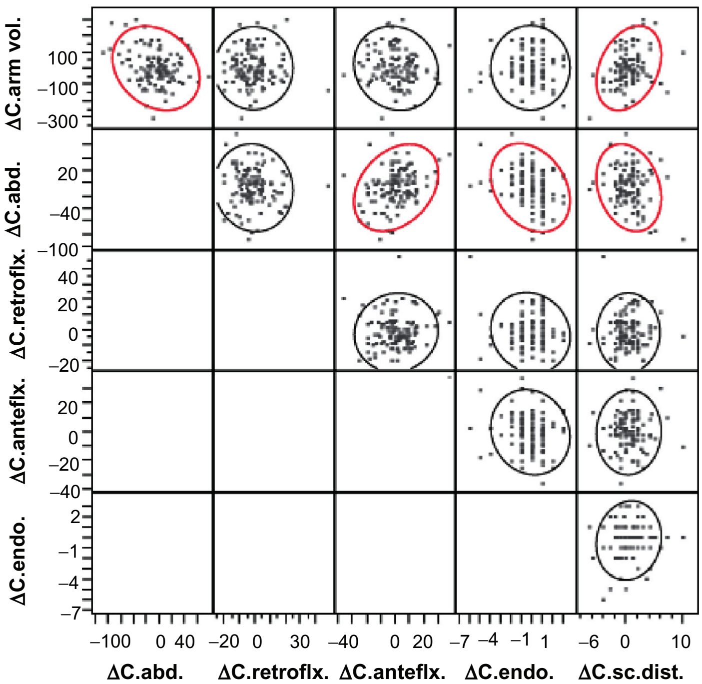

Figure 3. Correlations among contralateral shoulder-arm changes.
Notes: ΔC. = changes observed on the contralateral limb after breast radiotherapy, for measurements of abduction (abd.), retroflexion (retroflx.), anteflexion (anteflx.), endorotation (endo.), scapular distance (sc.dist.), and volume (vol.). Ellipses: 95% confidence density. Red colored ellipses indicate statistically significant correlations ($P \leq 0.05$).

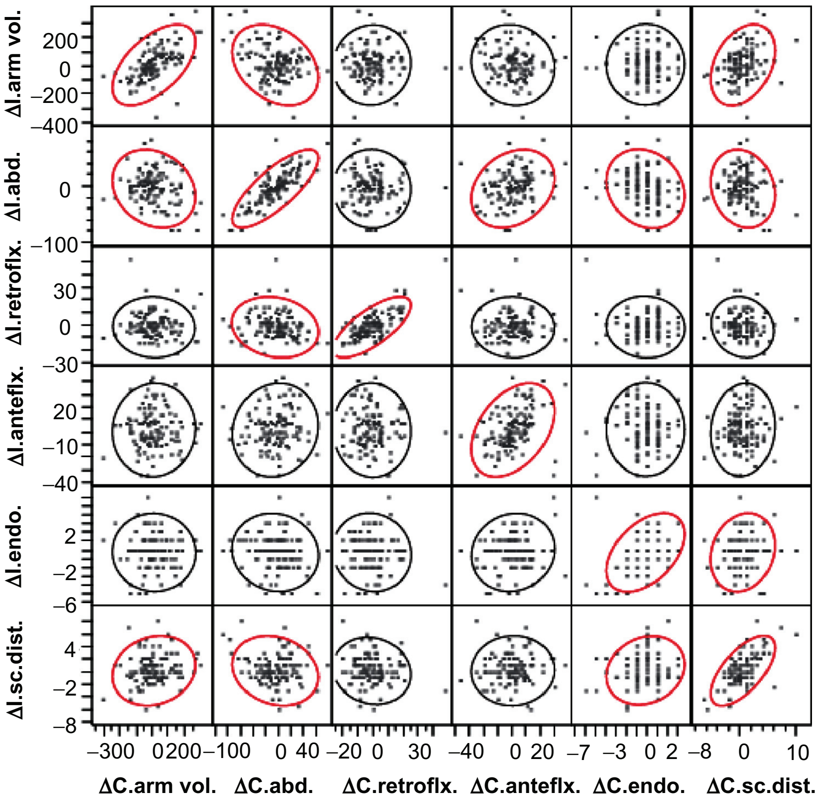

Figure 4. Correlations between ipsilateral and contralateral shoulder-arm changes.
Notes: Changes observed on the ipsilateral (ΔI.) and contralateral (ΔC.) limb after breast radiotherapy, for measurements of abduction (abd.), retroflexion (retroflx.), anteflexion (anteflx.), endorotation (endo.), scapular distance (sc.dist.), and volume (vol.). Ellipses: 95% confidence density. Red colored ellipses indicate statistically significant correlations ($P \leq 0.05$).

observation. However, we note a study of 144 breast cancer survivors reporting that women with lymphedema had bilaterally less elbow flexion strength and shoulder range of movement,[44] well in correspondance with the correlation of −0.32 between ipsilateral arm volume change and contralateral abduction (negative correlation: increase of arm volume correlates with decrease of abduction) (Table 3).

The regression analysis found aromatase inhibitor therapy as the only significant factor associated with contralateral loss of abduction (Table 4). In a comprehensive review, the incidence of musculoskeletal symptoms from 8 randomized clinical trials and 46,676 patients have been reported in up to 37.6% of aromatase inhibitor patients.[45] However, no study has reported physical therapy assessment in the evaluation of aromatase inhibitors.

Multiple other mechanisms can be invoked to explain contralateral loss of mobility, such as post-surgery changes of body posture at rest or during arm elevation, shoulder girdle misalignment, alterations of scapular kinematics.[28,46–49] The paradoxical effect of mastectomy that we found in the regression analysis, improved ipsilateral anteflexion and contralateral scapular distance (Table 4), suggests overcompensating mechanisms and would tend to support the hypothesis of altered scapular kinematics. Rotator cuff disease can also be invoked as part of the normal aging process, with breast cancer treatment exerting an additional stress on the degenerative tissues. However, even though the trial included elderly patients, age was not a significant factor in the regression analysis.

The presence of arm symptoms prior to RT was associated with improved ipsilateral mobility (Table 4). As part of the institution's standard surgical management, ambulatory physical therapy is prescribed to all operated breast cancer patients. We hypothesize that the presence of arm symptoms in our patients might have been a surrogate indicator of compliance, as symptomatic patients would have been more likely to seek physical therapy. Beurskens et al reported in a randomized study that symptomatic patients following breast cancer surgery and

Table 4. Risk factors of shoulder-arm changes from baseline.

Response variable	Model's adjusted *P*	Risk factor	Coefficient	Unadjusted *P*-value
Ipsilateral				
Δ arm volume	0.009	Δ weight	7.4	0.003
		ALND	61.5	0.004
Δ abduction	0.067	RT to regional nodes	–14.6	0.011
		Pre-RT arm symptoms	16.9	0.010
Δ retroflexion	–	–	–	–
Δ anteflexion	0.015	Mastectomy	8.8	0.004
		Pre-RT arm symptoms	8.3	0.021
Δ endorotation	0.019	Pre-RT arm symptoms	–1.4	0.001
Δ scapular distance	0.242	ALND	0.9	0.038
Contralateral				
Δ arm volume	0.034	Δ weight	6.6	0.005
		ALND	39.1	0.045
Δ abduction	0.188	Aromatase inhibitor therapy	–11.6	0.027
Δ retroflexion	–	–	–	–
Δ anteflexion	–	–	–	–
Δ endorotation	–	–	–	–
Δ scapular distance	0.144	ALND	1.3	0.006
		Mastectomy	–0.9	0.062
Relative				
Δ volume RID	–	–	–	–
Δ abduction RID	0.058	Pre-RT arm symptoms	10.0	0.006
Δ retroflexion RID	–	–	–	–
Δ anteflexion RID	0.009	Pre-RT arm symptoms	9.5	$<$0.001
Δ endorotation RID	–	–	–	–
Δ scapular distance RID	–	–	–	–

Notes: Adjusted *P* used false discovery control method of Benjamini and Yekutieli[36] with n comparisons equal to 18, the number of dependent response variables being evaluated.
Abbreviations: RT, radiation treatment; ALND, axillary lymph node dissection; RID, relative interlimb difference; Δ, change of measurement between baseline and first post-RT follow-up at 2 months; –, No risk factor identified, regression models were not improved with covariates.

axillary lymph node dissection who received physiotherapy within 3 months had significant improvement in shoulder mobility, but no significant difference of arm volume, as compared with patients who did not receive physiotherapy.[50] Our finding of a favorable relationship between presence of arm symptoms and shoulder mobility, but not with arm volume, is well in keeping with that study. However, we did not record the patients' compliance to receipt of physical therapy during the study.

There is a pitfall in the comparison of grouped measurement means as in Table 2. The lack of differences should not be equated with lack of toxicities. Figure 5 uncovers the underlying changes explaining why the comparison of means failed to detect differences. At baseline pre-RT 21% (blue bars) and 17% (brown bars) of the patients presented with grade 1 or more edema affecting the ipsilateral and the contralateral limb, respectively. At 2-months follow-up post-RT, the distributions of these patients shifted towards 0, indicating regression of their edema. But at the same time, other patients experienced new onset of edema: 14% on the ipsilateral limb (dark green bars), 12% on the contralateral limb (yellow bars). The changes of states suggests that arm swelling arises from different mechanisms, some possibly transient.[6,51] In any case, the comparison of means did not take into account what happened to individual patients and missed the changes.

We acknowledge several limitations to the present study. The TomoBreast trial was neither designed nor powered for the present explorative analyses. Pre-operative assessments were not done. Receipt of physical therapy during the course of the trial was

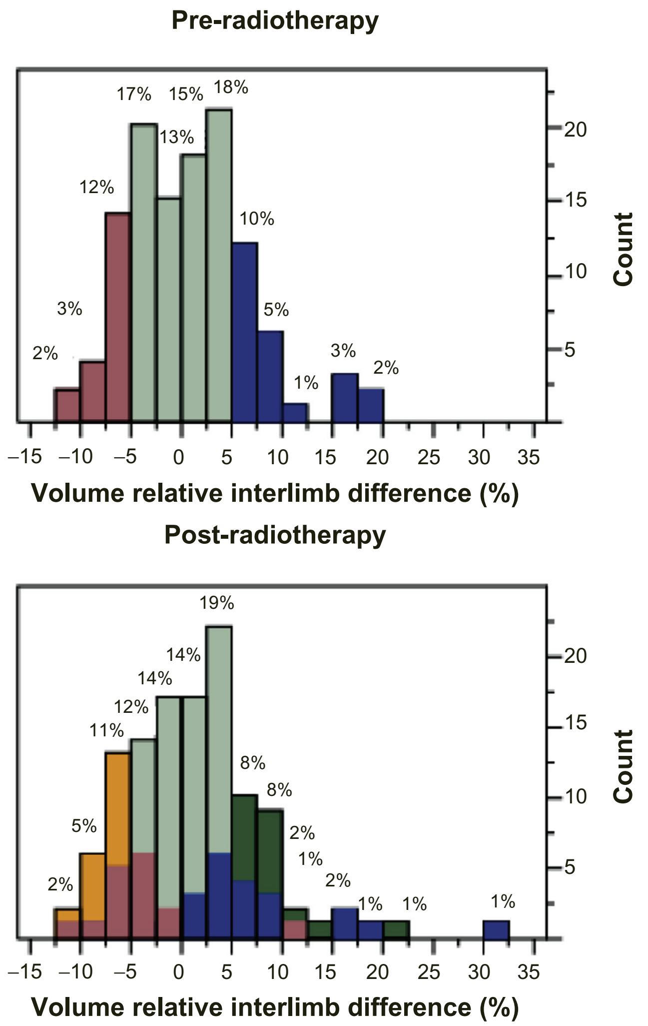

Figure 5. Distribution of volume relative interlimb difference (RID) at baseline and after radiotherapy (RT).

Notes: Top graph: At baseline pre-radiotherapy, 21% of the patients presented with limb edema, as defined by a volume RID of ≥5%. These patients are represented as blue bars. Bottom graph: Pre-radiotherapy, some patients improved (shift of the blue bars toward 0), some worsened (increase up to RID > 30). The dark green bars are patients who had no ipsilateral limb edema at baseline. The net result Pre-radiotherapy is an incidence of 24% patients with ipsilateral limb edema, composed of patients who had persistent edema (blue), minus those whose edema resolved, but incremented by patients with new onset of ipsilateral edema (dark green). Conversely, at baseline 17% of the patients presented with contralateral limb edema, shown as brown bars. Pre-radiotherapy, the incidence of contralateral limb edema is 18%. The 18% is composed of patients with prior contralateral edema that did not resolve (brown), incremented by patients with new onset of contralateral edema (yellow).

not monitored, although this could be considered as a strength, in effect the investigators were blinded to that treatment modality. We did not assess the reproducibility of arm and shoulder measurements, which could affect the reliability of the observations.[52] However, 83% of the measurements were made by the same physical therapist (NA), which helped to ensure consistency.[18] Quality of life assessments were not integrated into the analyses. The follow-up is short, the present study addresses only early morbidity, it cannot infer whether or not the findings will hold with longer follow-up.

Regarding the explorative analysis, our choice of the BIC as a selection criteria for regression might have been too stringent, excluding potentially clinically important variables. Nevertheless, we believe it ensured against "discovery overoptimism". Out of the 18 evaluated responses, only 10 were retained by the BIC (Table 4). Further penalizing for multiple outcomes using a relatively conservative method (see results with other methods in Supplementary data), only 5 of the responses would be retained with an adjusted P-value <0.05 (Table 4). Hence, associations such as between axillary dissection and impaired scapular distance or between aromatase inhibitor and loss of abduction should not be considered as firmly established.

In summary, the study builds on the strengths of a prospective clinical trial in which the patients' management and observation have been consistently assured by the same team, which we believe outweigh the limitations. While the explorative analysis should be considered only as hypothesis generating, the study found a high incidence of increased arm volume and shoulder mobility impairment affecting both arms. There are several potentially important implications. The findings argue that exclusive focus on the ipsilateral "affected" arm bears the risk of overlooking morbidity affecting the contralateral limb. Not recognizing contralateral limb impairment might delay its management. Comparisons assuming the contralateral limb as reference might underestimate toxicity, or conversely overestimate efficacy of ipsilateral limb treatment.[53] Further researches are needed to evaluate contralateral shoulder-arm morbidity.

Conclusion

We argue that conventional assessment based on comparison of operated side with non-operated side can underestimate the true severity of toxicity affecting one or both arms, or conversely overestimate efficacy of management of the affected limb. Assessment should not rely exclusively on interlimb differences but should also take into account serial measurements. High incidence of early morbidity affecting the contralateral arm warrants further investigations.

Author Contributions

Conceived and designed the experiments: NA, VVH. Analysed the data: NA, VVH. Wrote the first draft of the manuscript: NA, VVH. Contributed to the writing of the manuscript: NA, VVH, GM, HV, JL, MVa, PL, HVP, GS, MVo, MDR. Agree with manuscript results and conclusions: NA, VVH, GM, HV, JL, MVa, PL, HVP, GS, MVo, MDR. Jointly developed the structure and arguments for the paper: NA, VVH. Made critical revisions and approved final version: NA, VVH, GM, HV, JL, MVa, PL, HVP, GS, MVo, MDR. All authors reviewed and approved of the final manuscript.

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Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

References

1. International Agency for Research on Cancer. World cancer report. In: Boyle P, Levin B, editors. Lyon, France: *International Agency for Research on Cancer*. 2008.
2. National Cancer Institute. SEER Cancer Statistics Review, 1975–2008. Based on November 2010 SEER data submission, posted to the SEER web site, In: Howlader N, Noone A, Krapcho M, et al, editors. Bethesda, MD: 2011.
3. Lee TS, Kilbreath SL, Refshauge KM, Herbert RD, Beith JM. Prognosis of the upper limb following surgery and radiation for breast cancer. *Breast Cancer Res Treat*. 2008;110:19–37.
4. Levangie PK, Drouin J. Magnitude of late effects of breast cancer treatments on shoulder function: a systematic review. *Breast Cancer Res Treat*. 2009;116:1–15.
5. Shah C, Vicini FA. Breast Cancer-Related Arm Lymphedema: Incidence Rates, Diagnostic Techniques, Optimal Management and Risk Reduction Strategies. *Int J Radiat Oncol Biol Phys*. 2011.
6. Mortimer PS. The pathophysiology of lymphedema. *Cancer*. 1998;83:2798–802.
7. Bentzen SM, Dische S. Morbidity related to axillary irradiation in the treatment of breast cancer. *Acta Oncol*. 2000;39:337–47.
8. Arrault M, Vignes S. Risk factors for developing upper limb lymphedema after breast cancer treatment. *Bull Cancer*. 2006;93:1001–6.
9. Tsai RJ, Dennis LK, Lynch CF, Snetselaar LG, Zamba GK, Scott-Conner C. The risk of developing arm lymphedema among breast cancer survivors: a meta-analysis of treatment factors. *Ann Surg Oncol*. 2009;16:1959–72.
10. Ridner SH, Dietrich MS, Stewart BR, Armer JM. Body mass index and breast cancer treatment-related lymphedema. *Support Care Cancer*. 2011;19:853–7.
11. Tengrup I, Tennvall-Nittby L, Christiansson I, Laurin M. Arm morbidity after breast-conserving therapy for breast cancer. *Acta Oncol*. 2000;39:393–7.
12. Haines TP, Sinnamon P. Early arm swelling after breast surgery: changes on both sides. *Breast Cancer Res Treat*. 2007;101:105–2.
13. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). In: National Cancer Institute. 2006.
14. Voordeckers M, Van de Steene J, Vinh-Hung V, Storme G. Adjuvant radiotherapy after mastectomy for pT1-pT2 node negative (pN0) breast cancer: is it worth the effort? *Radiother Oncol*. 2003;68:227–31.
15. Voordeckers M, Vinh-Hung V, Van de Steene J, Lamote J, Storme G. The lymph node ratio as prognostic factor in node-positive breast cancer. *Radiother Oncol*. 2004;70:225–30.
16. Reynders T, Tournel K, De CP, et al. Dosimetric assessment of static and helical TomoTherapy in the clinical implementation of breast cancer treatments. *Radiother Oncol*. 2009;93:71–9.
17. Sitzia J. Volume measurement in lymphoedema treatment: examination of formulae. *Eur J Cancer Care (Engl)*. 1995;4:11–6.
18. Karges JR, Mark BE, Stikeleather SJ, Worrell TW. Concurrent validity of upper-extremity volume estimates: comparison of calculated volume derived from girth measurements and water displacement volume. *Phys Ther*. 2003;83:134–45.
19. Meijer RS, Rietman JS, Geertzen JH, Bosmans JC, Dijkstra PU. Validity and intra- and interobserver reliability of an indirect volume measurements in patients with upper extremity lymphedema. *Lymphology*. 2004;37:127–33.
20. Esch D, Lepley M. *Evaluation of Joint Motion: Methods of Measurement and Recording*. Minneapolis: University of Minnesota Press; 1974.
21. Eston RG, Reilly T. Part two: neuromuscular and goniometric aspects of movement, 6. Flexibility. In: *Kinanthropometry and Exercise Physiology Laboratory Manual: Tests*, *Procedure and Data*. 1990:115–21.
22. Duff M, Hill AD, McGreal G, Walsh S, McDermott EW, O'Higgins NJ. Prospective evaluation of the morbidity of axillary clearance for breast cancer. *Br J Surg*. 2001;88:114–7.

23. Cho J, Han W, Lee JW, et al. A scoring system to predict nonsentinel lymph node status in breast cancer patients with metastatic sentinel lymph nodes: a comparison with other scoring systems. *Ann Surg Oncol*. 2008; 15:2278–86.
24. Husted Madsen A, Haugaard K, Soerensen J, et al. Arm morbidity following sentinel lymph node biopsy or axillary lymph node dissection: a study from the Danish Breast Cancer Cooperative Group. *Breast*. 2008;17: 138–47.
25. Nesvold IL, Dahl AA, Lokkevik E, Marit MA, Fossa SD. Arm and shoulder morbidity in breast cancer patients after breast-conserving therapy versus mastectomy. *Acta Oncol*. 2008;47:835–42.
26. Shamley D, Srinaganathan R, Oskrochi R, Lascurain-Aguirrebena I, Sugden E. Three-dimensional scapulothoracic motion following treatment for breast cancer. *Breast Cancer Res Treat*. 2009;118:315–22.
27. Chan DN, Lui LY, So WK. Effectiveness of exercise programmes on shoulder mobility and lymphoedema after axillary lymph node dissection for breast cancer: systematic review. *J Adv Nurs*. 2010;66:1902–4.
28. Crosbie J, Kilbreath SL, Dylke E, et al. Effects of mastectomy on shoulder and spinal kinematics during bilateral upper-limb movement. *Phys Ther*. 2010;90:679–92.
29. Clark B, Sitzia J, Harlow W. Incidence and risk of arm oedema following treatment for breast cancer: a three-year follow-up study. *QJM*. 2005; 98:343–8.
30. Gartner R, Jensen MB, Kronborg L, Ewertz M, Kehlet H, Kroman N. Self-reported arm-lymphedema and functional impairment after breast cancer treatment—a nationwide study of prevalence and associated factors. *Breast*. 2010;19:506–15.
31. Helms G, Kuhn T, Moser L, Remmel E, Kreienberg R. Shoulder-arm morbidity in patients with sentinel node biopsy and complete axillary dissection—data from a prospective randomised trial. *Eur J Surg Oncol*. 2009;35:696–701.
32. Lievens P. Lymphedema or swelling? *Journal of Lymphoedema*. 2008;3: 17–9.
33. Nesvold IL, Fossa SD, Naume B, Dahl AA. Kwan's arm problem scale: psychometric examination in a sample of stage II breast cancer survivors. *Breast Cancer Res Treat*. 2009;117:281–8.
34. Boyd BS. Common Interlimb Asymmetries and Neurogenic Responses during Upper Limb Neurodynamic Testing: Implications for Test Interpretation. *J Hand Ther*. 2012;25:56–64.
35. Burnham KP, Anderson DR. Multimodel inference: understanding AIC and BIC in model selection. *Sociological Methods and Research*. 2004;33: 261–304.
36. Benjamini Y, Yekutieli D. The control of the false discovery rate in multiple testing under dependency. *The Annals of Statistics*. 2001;29:1165–88.
37. The R Foundation for Statistical Computing. R version 2.14.1 (2011-12-22). *The Comprehensive R Archive Network* December 2011. Available at: http://cran.r-project.org/index.html. Accessed January 4, 2012.
38. Voordeckers M, Vinh-Hung V, Lamote J, Bretz A, Storme G. Survival benefit with radiation therapy in node-positive breast carcinoma patients. *Strahlenther Onkol*. 2009;185:656–62.
39. Adriaenssens N, Van Parijs H, Miedema G, et al. Preliminary analysis of a randomized clinical trial comparing shoulder-arm morbidity between early breast cancer patients treated with short course image guided radiation therapy and conventional post surgery radiation therapy. *The Journal of Breast Health*. 2012.
40. Stout Gergich NL, Pfalzer LA, McGarvey C, Springer B, Gerber LH, Soballe P. Preoperative assessment enables the early diagnosis and successful treatment of lymphedema. *Cancer*. 2008;112:2809–19.
41. Perre CI, Hoefnagel CA, Kroon BB, Zoetmulder FA, Rutgers EJ. Altered lymphatic drainage after lymphadenectomy or radiotherapy of the axilla in patients with breast cancer. *Br J Surg*. 1996;83:1258.
42. Fontaine C, Adriaenssens N, Van Parijs H, et al. A propsective analysis of the incidence of breast cancer related lymphedema of the arm after surgery and axillary lymph node dissection in early breast cancer patients treated with concomitant irradiation and anthracyclines followed by paclitaxel. *European Journal of Lymphology*. 2011;22:20–4.
43. Caers J, Fontaine C, Vinh-Hung V, et al. Catheter tip position as a risk factor for thrombosis associated with the use of subcutaneous infusion ports. *Support Care Cancer*. 2005;13:325–31.
44. Smoot B, Wong J, Cooper B, et al. Upper extremity impairments in women with or without lymphedema following breast cancer treatment. *J Cancer Surviv*. 2010;4:167–78.
45. Dent SF, Gaspo R, Kissner M, Pritchard KI. Aromatase inhibitor therapy: toxicities and management strategies in the treatment of postmenopausal women with hormone-sensitive early breast cancer. *Breast Cancer Res Treat*. 2011;126:295–310.
46. Borstad JD. Resting position variables at the shoulder: evidence to support a posture-impairment association. *Phys Ther*. 2006;86:549–57.
47. Rostkowska E, Bak M, Samborski W. Body posture in women after mastectomy and its changes as a result of rehabilitation. *Adv Med Sci*. 2006;51: 287–97.
48. Malicka I, Barczyk K, Hanuszkiewicz J, Skolimowska B, Wozniewski M. Body posture of women after breast cancer treatment. *Ortop Traumatol Rehabil*. 2010;12:353–61.
49. Ebaugh D, Spinelli B, Schmitz KH. Shoulder impairments and their association with symptomatic rotator cuff disease in breast cancer survivors. *Med Hypotheses*. 2011;77:481–7.
50. Beurskens CH, van Uden CJ, Strobbe LJ, Oostendorp RA, Wobbes T. The efficacy of physiotherapy upon shoulder function following axillary dissection in breast cancer, a randomized controlled study. *BMC Cancer*. 2007;7:166.
51. Werner RS, McCormick B, Petrek J, et al. Arm edema in conservatively managed breast cancer: obesity is a major predictive factor. *Radiology*. 1991;180:177–84.
52. May S, Chance-Larsen K, Littlewood C, Lomas D, Saad M. Reliability of physical examination tests used in the assessment of patients with shoulder problems: a systematic review. *Physiotherapy*. 2010;96:179–90.
53. Mayrovitz HN, Macdonald J, Davey S, Olson K, Washington E. Measurement decisions for clinical assessment of limb volume changes in patients with bilateral and unilateral limb edema. *Phys Ther*. 2007;87:1362–8.

Supplementary Data

Table S1. Adjusted *P*-values according to different methods.

Response variable	Unadjusted *P* of full model	Order index j of the unadjusted *P*'s	Simes' j*alpha/ unadjusted *P*	Simes' compared with unadjusted *P*	Hommel's adjusted *P*	Benjamini 2001's adjusted *P*	Benjamini 1995's adjusted *P*
ipsil_Δ arm volume	0.0003	2	0.0056	True	0.0051	0.009	0.003
ipsil_Δ abduction	0.0074	7	0.0194	True	0.0888	0.067	0.019
ipsil_Δ retroflexion	–						
ipsil_Δ anteflexion	0.0007	3	0.0083	True	0.0105	0.015	0.004
ipsil_Δ endorotation	0.0012	4	0.0111	True	0.018	0.019	0.005
ipsil_Δ scapular distance	0.0384	10	0.0278	False	0.3456	0.242	0.069
contr_Δ arm volume	0.0027	5	0.0139	True	0.0351	0.034	0.010
contr_Δ abduction	0.0269	9	0.0250	False	0.2421	0.188	0.054
contr_Δ retroflexion	–						
contr_Δ anteflexion	–						
contr_Δ endorotation	–						
contr_Δ scapular distance	0.0183	8	0.0222	True	0.183	0.144	0.041
Δ volume RID	–						
Δ abduction RID	0.0055	6	0.0167	True	0.066	0.058	0.017
Δ retroflexion RID	–						
Δ anteflexion RID	0.0002	1	0.0028	True	0.0034	0.009	0.003
Δ endorotation RID	–						
Δ scapular distance RID	–						