SYMPTOMS AND LIMB CHANGES IN BREAST CANCER SURVIVORS TREATED WITH NEOADJUVANT CHEMOTHERAPY: LYMPHEDEMA RESULTS OF ACOSOG Z1071 (ALLIANCE)

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INTRODUCTION

- There are about 2.9 million breast cancer survivors in US.
- Research shows one-third to one-half of breast cancer survivors will develop upper extremity lymphedema (LE) during their lifetimes.[1]
- LE is defined as an accumulation of fluid with high protein concentrations in the interstitial spaces.[2]
- Post-breast cancer-related LE follows breast cancer treatment (mastectomy, lumpectomy, axillary dissection, sentinel lymph node surgery, chemotherapy, radiation, or other trauma).[3]
- The ACOSOG Z1071 trial patients with treated neoadjuvant chemotherapy followed by breast surgery and axillary dissection +/- radiation.[4]
- Patients enrolled in the trial were eligible for this longitudinal substudy evaluating LE.
- Limb volume, circumferences, and symptom assessments were measured at baseline prior to surgery and at 6 follow-up visits over 36 months to examine the rate of breast cancer-related LE.

METHODS

Eligibility Criteria

Women older than 18 years old who had:

- cT0-T4,N1-2, M0 according to the American Joint Committee on Cancer 7th edition staging system[5]
- Fine-needle aspiration or core needle biopsy of an axillary node documenting nodal disease at time of diagnosis (prior to pre-operative chemotherapy)
- No prior ipsilateral axillary surgery, no prior SLN surgery/excisional lymph node biopsy for pathological confirmation of axillary status

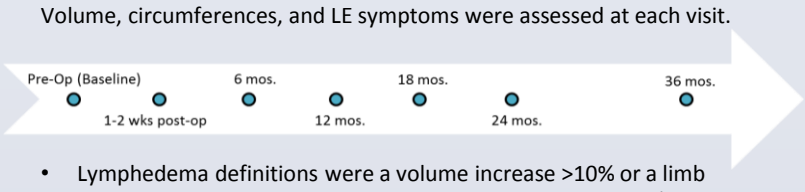
Women were excluded who had:

- Bilateral breast cancer
- Current limb infection or lymphangitis
- Any condition that would affect LE assessment

Only patients with lymphedema data were included in this analysis.

Assessment of LE

Volume, circumferences, and LE symptoms were assessed at each visit.



- Lymphedema definitions were a volume increase >10% or a limb circumference increase >2cm, as compared to baseline and/or the contralateral limb.[6,7]
- Limb volume changes were measured by circumferences at five anatomic locations, with volume calculated using the truncated cone formula.[5]
- Symptoms were assessed by the Lymphedema Breast Cancer Questionnaire (LBCQ) via interview.[7,8] There are 19 symptoms that are components of the LBCQ LE assessment.

Statistical analysis

The database used for these analyses was locked May 1, 2013. Statistical analyses were carried out using SAS (SAS Institute Inc, version 9.2).

RESULTS

Lymphedema data were available on 488 patients with median age 49 years (range 23–78), comprising 70% of the parent study (n=701).

Table 1: Rates of lymphedema over time

	Baseline	1-2 weeks	6 months	12 months	18 months	24 months	36 months	3-year Cumulative Incidence (95% CI)
10% limb volume increase	---	73/365 (20.0%)	101/347 (29.1%)	112/305 (36.7%)	96/272 (35.3%)	90/249 (36.1%)	82/203 (40.4%)	60.3% (55.0% - 66.2%)
>2cm circumference increase	---	125/383 (32.6%)	159/362 (43.9%)	146/322 (45.3%)	136/287 (47.4%)	135/261 (51.7%)	96/211 (45.5%)	75.4% (70.8% - 80.2%)
Arm heaviness symptom	27/409 (6.6%)	105/427 (24.6%)	52/402 (12.9%)	55/355 (15.5%)	44/318 (13.8%)	35/288 (12.2%)	27/232 (11.6%)	25.6% (21.3% - 30.6%)
Arm swelling symptom	13/411 (3.2%)	100/426 (23.5%)	51/403 (12.7%)	66/358 (18.4%)	52/318 (16.4%)	47/287 (16.0%)	34/233 (14.6%)	30.9% (26.3% - 36.3%)

At 36 months post-surgery, lymphedema incidence was:

- 60.3% (95% CI: 55.0%-66.2%) by the criterion of ≥10% limb volume increase
- 75.4% (95% CI: 70.8%-80.2%) by ≥2cm circumference increase criterion

Arm heaviness and arm swelling had a 3-year 25-31% cumulative incidence, respectively.

Lymphedema symptoms were relatively stable after 18 months.

RESULTS (continued)

Table 2: Concordance of lymphedema measures (10% vs 2cm increase)

Lymphedema by 10% volume increase	Lymphedema by any location 2 cm increase	
	Yes	No
Yes	178 (63.4%)	33 (30.6%)
No	103 (36.6%)	75 (69.4%)

Kappa=0.27 (95% CI: 0.18 – 0.36) p<0.0001

- Weighted kappa coefficient was 0.27 (95% CI: 0.18-0.36), indicating modest agreement between the two criteria (see Table 2).
- There was limited agreement with weighted kappa coefficients (0.05-0.09), comparing volume or ≥2cm increase to reported heaviness and/or swelling.

Table 3. Number of Patients Reporting Multiple Lymphedema Symptoms

Number of Symptoms	Baseline n=387	1-2 wks n=402	6 mos n=380	12 mos n=342	18 mos n=302	24 mos n=277	36 mos n=220
0	245 (63.3%)	49 (12.2%)	103 (27.1%)	131 (38.3%)	142 (47.0%)	137 (49.5%)	112 (50.9%)
1	59 (15.2%)	36 (9.0%)	66 (17.4%)	58 (17.0%)	49 (16.2%)	41 (14.8%)	38 (17.3%)
2-5	57 (14.7%)	128 (31.8%)	126 (33.2%)	95 (27.8%)	66 (21.8%)	54 (19.5%)	40 (18.2%)
6+	26 (6.7%)	189 (47.0%)	85 (22.4%)	58 (17.0%)	45 (14.9%)	45 (16.2%)	30 (13.6%)
1 or more	142 (36.7%)	353 (87.8%)	277 (72.9%)	211 (61.7%)	160 (53.0%)	140 (50.5%)	108 (49.1%)

- Three-fifths (63.3%) of participants reported 'no symptoms' at baseline pre-operatively (Table 3). One-tenth as many (6.7%) experienced '6 or more symptoms' at baseline.
- Eighty-eight percent reported '1 or more symptoms' at post-op (1-2 weeks after surgery), with one-fifth (22.5%) reporting '6 or more symptoms'.
- Half of participants (50.9%) reported 'no symptoms' at 36 months, whereas 1 in 6 (13.6%) reported 'six or more symptoms' at 36 months.
- Although a small number of participants, the percentage with '6 or more symptoms' doubled from baseline to 36 months.
- Overall, presence of 'any symptoms' gradually decreased from post-op (87.8%) to 36 months (49.1%).

CONCLUSIONS

- **Incidence of limb volume and circumference changes meeting the criteria for lymphedema gradually increased over 36 months.**
  - Lymphedema symptoms decreased from post-op over 18 months after surgery, thereafter remaining stable.
  - Findings underscore the value of *prospective clinical surveillance* from pre-op to 36 months.
- **Reported occurrence of lymphedema is dependent on the criteria applied.**
  - The criterion of ≥10% volume chance compared to baseline and contralateral limb volume change is a slightly more conservative measure of whole-limb volume change.
  - ≥2 cm circumference change in arm girth at any anatomic point is perhaps 'too sensitive' for identifying whole-limb change.
  - We recommend the >10% volume change criterion be used for future analysis of these Z1071 data and other clinical trials.
  - More sensitive volume change (5%) or girth change may be used for early detection and referral to lymphedema specialist care.
- **We highly recommend the inclusion of both an *objective and subjective measure* for lymphedema assessment** in the prospective surveillance model and in clinical practice, since objective measures (limb volume and girth) of lymphedema are not always highly correlated with subjective measures (such as symptom report).

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