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CRITICAL REVIEW

BREAST CANCER-RELATED ARM LYMPHEDEMA: INCIDENCE RATES, DIAGNOSTIC TECHNIQUES, OPTIMAL MANAGEMENT AND RISK REDUCTION STRATEGIES

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As more women survive breast cancer, long-term toxicities affecting their quality of life, such as lymphedema (LE) of the arm, gain importance. Although numerous studies have attempted to determine incidence rates, identify optimal diagnostic tests, enumerate efficacious treatment strategies and outline risk reduction guidelines for breast cancer–related lymphedema (BCRL), few groups have consistently agreed on any of these issues. As a result, standardized recommendations are still lacking. This review will summarize the latest data addressing all of these concerns in order to provide patients and health care providers with optimal, contemporary recommendations.

Published incidence rates for BCRL vary substantially with a range of 2–65% based on surgical technique, axillary sampling method, radiation therapy fields treated, and the use of chemotherapy. Newer clinical assessment tools can potentially identify BCRL in patients with subclinical disease with prospective data suggesting that early diagnosis and management with noninvasive therapy can lead to excellent outcomes. Multiple therapies exist with treatments defined by the severity of BCRL present. Currently, the standard of care for BCRL in patients with significant LE is complex decongestive physiotherapy (CDP).

Contemporary data also suggest that a multidisciplinary approach to the management of BCRL should begin prior to definitive treatment for breast cancer employing patient-specific surgical, radiation therapy, and chemotherapy paradigms that limit risks. Further, prospective clinical assessments before and after treatment should be employed to diagnose subclinical disease. In those patients who require aggressive locoregional management, prophylactic therapies and the use of CDP can help reduce the long-term sequelae of BCRL. © **2011 Elsevier Inc.**

Breast cancer, Lymphedema, Risk reduction, Management strategies.

INTRODUCTION

The incidence of breast cancer in the United States is approximately 200,000 cases per year with an estimated prevalence of 2.4 million women (1). As survival increases in early stage and locally advanced breast cancers, long-term toxicities affecting quality of life, including lymphedema (LE) of the arm, gain greater significance. Estimates of the rate of LE vary significantly from less than 5% with lumpectomy alone to more than 60% when treatment includes axillary lymph node dissection and axillary radiation with up to 800,000 women having some form of LE based on current prevalence rates (2).

Numerous studies have attempted to determine *1*) the true incidence rate of breast cancer related lymphedema (BCRL) based on therapeutic modality employed; *2*) the optimal clinical assessment tools required to objectively and consistently support clinician diagnosis and monitoring of the condition; *3*) efficacious evidence-based treatment strategies to control, improve or prevent the progression of BCRL; and *4*) risk-reduction strategies. Unfortunately, there is a lack of consensus on many of these issues and as a result standardized guidelines are still lacking.

GRADING AND INCIDENCE OF BCRL

Multiple scales have been devised to categorize LE in order to objectively compare incidence rates and to better evaluate treatment efficacy. The LENT/SOMA scale uses 4 grades (Grade 1: 2–4 cm, Grade 2: 4–6 cm, Grade 3: >6 cm, and Grade 4: nonfunctional arm) based on circumference measurements (3). More recently, the Common Terminology Criteria for Adverse Events, v.4.03, has been released and has three grades of lymphedema (summarized in Table 1) (4).

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Table 1. CTC staging of lymphedema

Grade	Characteristics
1	Faint discoloration
	Trace thickening
2	Marked discoloration
	Leathery texture
	Papillary formation
	Limiting instrumental activities of daily living
3	Severe symptoms
	Limiting self-care activities of daily living

Significant variation exists in the reported incidence rates of BCRL from less than 5% with lumpectomy alone to more than 60% when treatment includes axillary lymph node dissection and axillary radiation. Historical estimates of LE rates can be obtained from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial, which randomized patients to radical mastectomy (Halsted procedure) versus total mastectomy with axillary radiation versus total mastectomy alone. The rates of LE as defined as an increase of 2 cm or more in arm circumference were 58.1%, 38.2%, and 49.1% for the radical mastectomy, total mastectomy and axillary radiation, and total mastectomy arms, respectively. The risk of severe LE (>4 cm increase) was 21.5%, 11.4%, and 13.1%, respectively (5). As surgical procedures have evolved and an increase in breast conserving therapy has emerged, the rates of BCRL published in the literature have varied and depend on the surgical procedure performed, the method of axillary surgery (sentinel lymph node biopsy vs. axillary lymph node dissection), the use of adjuvant radiation therapy, and the delivery of adjuvant chemotherapy.

A series of 3253 patients from Denmark evaluated the incidence of BCRL in patients undergoing: *1*) breast conservation (BC) with lumpectomy, sentinel lymph node assessment (SLN) and breast radiation; *2*) lumpectomy, axillary lymph node dissection (ALND), and breast radiation; or *3*) lumpectomy with radiation therapy to the breast and regional lymph nodes. The rates of LE for the three groups were 13%/23% (no chemotherapy administered/chemotherapy administered) for BC with SLN, 51%/61% for BC with ALND, and 53%/65% for BC with lymph node irradiation. The same study evaluated rates of LE with mastectomy with SLN, mastectomy with ALND, and mastectomy with chest wall and regional nodal irradiation and found the rates of LE to be 13%/23%, 42%/47%, and 58%/65%, respectively. Of note, in this study 50% of the patients had light LE (per 10-point scoring system, scores 1–3) and 38% moderate (scores 4–7) (2).

More recently, SLN biopsy has replaced ALND in patients who present with clinically node negative disease. NSABP B-32 randomized patients to SLN biopsy versus SLN biopsy followed by ALND. Prospective assessment of LE was performed with arm volume differences of 10% or greater characterized as BCRL. At all time intervals (6, 12, 18, 24, 30, and 36 months), the rates of BCRL were significantly less with SLN than ALND, and were 8% versus 14% at 36 months (6). This has been confirmed by data from Cornell University, which found the rates of BCRL to be 34.8% with ALND compared with 4.6% in SLN in a group of 265 patients with Stage I-II breast cancer with more than 10 years of follow-up (7). Table 2 presents data on the risk of LE by treatment characteristics (2, 5–19).

Table 2. Incidence of lymphedema stratified by surgical procedure, axillary management, and RT

Procedure	Risk of lymphedema (%)
Lumpectomy alone (9, 10)	0–3
Lumpectomy with SLN and breast RT (2, 6, 7, 14, 15, 18, 19)	3–23
Lumpectomy with ALND and breast RT (2, 6, 7, 11, 13, 14, 15, 16, 17)	1–61
Lumpectomy with regional nodal RT (2)	9–65
Mastectomy with SLN, no RT (2, 18, 19)	3–23
Mastectomy with ALND, no RT (2, 5, 17)	30–47%
Mastectomy with regional nodal RT (2, 5)	58–65
ALND with axillary RT (12)	32
Radical mastectomy (5)	58

Abbreviations: ALND = axillary lymph node dissection; SLN = sentinel lymph node; RT = radiation therapy.

Analysis of the NSABP B-04 trial found that an increased body mass index was associated with an increased risk of BCRL, which has subsequently been confirmed by multiple series (5, 20). A univariate analysis performed by Gartner *et al.* on more than 3,000 subjects found younger age, mastectomy, ALND, radiation therapy, and the receipt of chemotherapy to be significantly associated with the development of LE (2). The role of regional nodal irradiation in the development of BCRL has been confirmed in multiple studies. A review from Harvard University evaluated 727 patients treated with BC with or without the inclusion of regional lymphatics in the radiation treatment fields. The rate of BCRL (>2 cm difference in forearm circumference) was 2% with tangents alone and 9% with regional nodal volumes included, with the only predictor of BCRL being receipt of axillary radiation (11). An evaluation of axillary boost was performed by Hayes *et al.*, who examined the rates of LE in 2,579 women who received RT to the breast, breast and supraclavicular region, or breast, supraclavicular region, and axilla with a posterior axillary boost. The rates of LE were 16%, 23%, and 31%, respectively, with the addition of regional nodal irradiation, obesity, chemotherapy, and the number of nodes dissected found to be predictors for the development of BCRL (21). Table 3 presents published rates of BCRL based on radiation therapy modality delivered (2, 5, 11, 20, 22, 23).

The role of chemotherapy and LE has been confirmed by the Danish and Fox Chase Cancer Center studies as well as data from the University of Pennsylvania, which found that patients receiving chemotherapy had a hazard ratio of 1.46 for the development of LE (24).

DIAGNOSIS OF BCRL

The diagnosis of BCRL remains a challenge with many women who suffer from BCRL remaining undiagnosed until the condition causes significant morbidity. With studies demonstrating a benefit to early management, most authors