

IS SENTINEL LYMPH NODE BIOPSY A REAL HOPE IN THE PREVENTION OF BREAST CANCER-RELATED LYMPHEDEMA?

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More than 84 % of women with invasive breast cancer now survive more than five years. Chronic complications and disabilities such as lymphedema that occur as a result of therapeutic interventions became a major concern in those long-term survivors causing a significant decrease in their quality of life. In this review, we evaluate the impact of sentinel lymph node biopsy upon the prevention of lymphedema in light of both recently published studies and our own experience.

Breast cancer (BC) is one of the leading causes of death in women all over the world, and the incidence of this disease has been increasing for several decades. By the year 2005, the estimated number of new BC cases among females will be 211,240 in the United States (1). However, since its peak in 1990, BC mortality has declined by about 2.3% per year as a consequence of both early detection and widespread application of effective therapeutic modalities (1). Currently, women with BC have a five-year overall survival rate of 84% or more (2-4). On the other hand, chronic complications and disabilities that result from therapeutic interventions (surgery, radiation therapy, etc) became a major concern in those long-term survivors and cause a significant decrease in their quality of life (5-7).

Lymphedema of the upper arm is an often recognized but a usually neglected complication of BC therapy. The incidence of BC-related lymphedema varies greatly depending on its clinical definition, patient characteristics, measurement techniques, and the follow up time. Petrek and Heelan recently reported that 6%-30% of patients are suffering from lymphedema after BC treatment. This means that at least 12,684 and as many as 63,372 new cases (women) with BC are at risk of this troublesome complication in the US in 2005 (1,8). Causative factors for BC-related lymphedema could be grouped into three main categories: disease-, patient-, and treatment-related factors (9) (Table 1). Among them, surgical trauma is one of the leading reasons associated with development of lymphedema. Axillary lymph node dissection (ALND) has been an important part of standard surgical therapy and staging procedure for BC. However, a novel approach is the use of sentinel lymph node biopsy (SLNB) as a minimally invasive technique instead of classical ALND. This technique is less extensive and appears to have less severe complication rates than ALND. In this overview, we evaluate the impact of SLNB in the prevention of

BC-related lymphedema in light of both some recently published studies and our own experiences.

Pathophysiology of Lymphedema

Lymphedema is an abnormal collection of protein-rich fluid within soft tissues that occurs as a result of impaired lymphatic drainage. It is characterized by chronic inflammation and fibrosis, and usually occurs when lymph volume exceeds the functional capacity of lymphatic channels (10). Primary lymphedema is a rare abnormality usually due to either congenital absence or malformation of lymphatic system. Secondary lymphedema is a more common condition and is caused by physical interruption or mechanical obstruction of lymphatic channels as a consequence of previous surgery, irradiation, malignancy or infection.

Lymphatic drainage of the arm is primarily carried out by axillary lymph nodes and their related lymphatic channels. The traditional causal theory for BC-related lymphedema is the iatrogenic interruption of these lymphatic channels by surgery or radiation therapy leading to an outflow obstruction and extracellular fluid accumulation. However, the exact pathogenesis of lymphedema is not yet completely understood, and it would be an oversimplification to ascribe by swelling solely to vessel obliteration or interruption. Lymphedema does not occur in all BC patients treated in a similar manner. Thus, some other factors, which cause either inadequate drainage or overproduction of lymph fluid, may also play a role. In some patients, well-developed lymphovenous shunts might prevent lymphedema (11). Arm swelling may occur due to increased filtration from the vascular bed that occurs as a result of hemodynamic changes in the upper extremity blood vessels and their flow patterns. A recent study showed that 70% of patients with BC-related lymphedema have venous flow abnormalities includ-

Table1. Etiologic factor of breast cancer-related lymphedema

Disease-related factors:	Tumor stage, nodal status, location of tumor
Patient-related factors:	Age, obesity, hypertension, history of infection and inflammation, excessive use of the limb, time interval since treatment
Treatment-related factors:	Type of surgery, radiation therapy, other adjuvant therapeutic modalities.

ing outflow obstruction in their ipsilateral axilla subclavian region while they retain normal venous flow patterns kept in their contralateral arms (12). Another study demonstrated increased arterial inflow by Doppler ultrasound in BC-related lymphedema patients (13). Mortimer concluded in his recent review that not only does impaired lymphatic flow lead to lymphedema, but also that vascular factors such as increased total limb blood flow and increased size of capillary filtration area play important roles in the pathogenesis of breast-cancer related lymphedema (14). Stantan et al. emphasized that lymphatic collectors in the arm must work much harder than before surgery because of increased resistance occurs due to scarring (15). However, some lymphatic collectors are able to cope with this extra lymph flow but some are not. Thus, lymphatic flow obstruction develops behind the failing collector vessels. This appears to be closely related to a total pump failure of the lymphatic system associated with the additive effect of increased arm blood flow and capillary filtration. Surgical interventions play a major role in the process that leads to pump failure. Another important factor affecting incidence of lymphedema after breast surgery is body weight. There is evidence that body mass index (BMI) greater than 25 increases lymphedema (16-19).

Recently, VEGFR-3 and FOXC2 gene mutations have been identified in primary lymphedema cases (20, 21). The discoveries of lymphangiogenic growth factors vascular endothelial growth factor (VEGF)-C and VEGF-D and of their receptor, VEGFR-3 and FOXC2, on lymphatic endothelial cells have demonstrated that lymphatic molecular markers and growth factors are necessary for lymphangiogenesis (22, 23). They play crucial roles in stimulating lymphatic vascular growth both during development and in pathological conditions and offer the possibility of transcriptional reprogramming of vascular endothelial cells for future therapeutic applications (24, 25). Also it is possible that identification of genetic mutations in women at high risk of lymphedema would help to avoid this complication before treatment and to give us an opportunity to treat them during subsequent follow-up visits.

Impact Of Surgery On Lymphedema

At the end of 19th century, surgery was the major component of BC treatment. The paradigm of Halsted was that BC is mainly a local disease and disseminates via regional routes including lymph nodes and this led to extended resections with curative intent (26). Under this assumption, the majority of BC patients were treated with radical mastectomy (RM) before 1970s (27). Although RM was found to prevent local recurrence and to have longer survival but higher complication rates associated with this procedure have limited its use. Halsted first described lymphedema as one of the most troublesome complications of radical mastectomy and in 1921 named it "elephantiasis chirurgica" (28). Lymphedema has been a major concern throughout the historical development of BC surgery (Figure. 1). Haagensen reported a 13% incidence of lymphedema 10 years after RM (29). However, Britton and Nelson postulated in their meta-analysis that post mastectomy lymphedema of upper arm occurred in 6.7% to 62.5% of patients (30). In

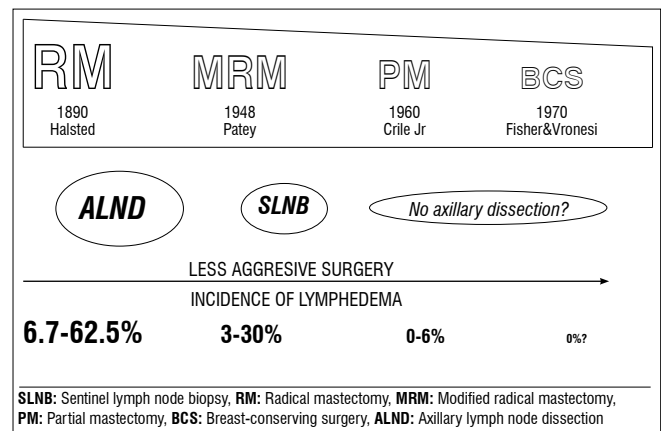


Figure 1. Historical development of breast cancer surgery

the 1960s, average rates of lymphedema were approximately 50% in several published series (31).

After its description in 1948 by Patey modified radical mastectomy (MRM) was popularized through the 1970s (32). It was reported that RM was associated with a higher incidence of lymphedema than MRM (42% versus 27%, respectively) (33). Golematis et al. reported a 5.5% lymphedema rate after MRM (34). Schunemann, in his large series with 5,868 patients, reported a lymphedema incidence of 22.3% in RM patients, 19.1% in MRM patients, and 6.7% after breast preserving operations (35). He also noted that in the 1970s, when the RM plus radiotherapy was the standard treatment for BC management, lymphedema incidence was 38%.

Today, modern BC treatment is breast-conserving surgery (BCS), which is less radical but not devoid of side effects. The necessity of postoperative radiotherapy after BCS is an important factor that significantly increases the risk of lymphedema. The incidence of lymphedema was reported to be 12% in a study that included 206 patients with stage I and stage II BC treated by wide excision plus axillary dissection and radiotherapy (36). In another study, two-thirds of the patients treated by BCS and radiotherapy developed lymphedema within the first two years (37). Meric et al. reported a 13.6% incidence of arm edema in their 294 patients treated with BCS plus radiotherapy and was 15% in the lumpectomy plus ALND group and 3% in the lumpectomy only group during a median follow-up period of 89 months (38). In this study arm swelling was more common in obese patients, but there was no relationship with histological positive lymph nodes, patient age, pathologic or clinical tumor size, adjuvant chemotherapy, or irradiation (18% vs. 10%, p=.07).

The removal of the axillary lymph nodes has been a standard part of BC treatment more than a century. Although ALND provides useful information for staging, treatment planning and local disease control, it also carries a substantial risk for lymphedema formation. Precise surgical technique might be an important factor in the prevention of this devastating complication. Gentle handling of tissues around axillary vessels and preservation of areolar

Table 2. The impact sentinel lymph node biopsy on lymphedema incidence in published studies

Author	N	Type	Lymphedema (%)	Follow up (Months)	Objective/ Subjective
Schrenk et al. ⁵²	35	Prospective	0	16 (4-28)	Arm measurement + subjective
Sener et al. ⁵³	303	Prospective	3	19	Arm measurement
Giuliano et al. ⁵⁴	125	Prospective	0	39(24-51)	Physical examination
Temple et al. ⁵⁵	233	Prospective	0	12	Arm measurement
Burak et al. ⁵⁶	98	Prospective	Less frequent	15.3 (8-29)	Arm measurement + subjective
Blanchard et al. ⁵⁷	894	Retrospective	6	29	Subjective
Schicven et al. ⁵⁸	393	Retrospective	1.1	12-36	Subjective
Golshan et al. ⁵⁹	125	Retrospective	2.6	>12	Arm measurement

tissue around the axillary vein are important considerations. A transverse incision not extending beyond the axillary line is also an important preventive measure advised by some authors (39, 40). However, the ideal goal should be to find a better surgical technique that eliminates the necessity of ALND. Various methods from full axillary dissection to lymphatic sampling have been used for this purpose, but none of them demonstrated significant success (41, 42). SLNB has now become an important alternative to ALND.

Sentinel Lymph Node Biopsy (SLNB)

SLNB is a minimally invasive surgical technique that has become an alternative procedure to ALND in BC staging. The sentinel node is defined as the first node to receive lymphatic drainage from a tumor. SLNB was introduced first by Cabanas as a staging procedure for penile cancer (43). The same concept was then extended to malignant melanoma (44). One year later, in 1993, Krag et al. published their study using sentinel lymph node biopsy for staging breast carcinoma (45). Either a dye-guided or a gamma probe-guided method can identify the sentinel lymph node (SLN). Identification of the SLN is facilitated when both techniques are used together, and there has been a tendency to use a combination of the radioisotope and blue dye to increase the detection rate of the SLN (46-48). Albertini first reported the combination technique by using ^{99m}Tc sulfur colloid and isosulfan blue dye (49).

The major advantage of SLNB is that it may reduce lymphedema by decreasing the number of unnecessary ALND. However, surgeons who are beginning lymphatic mapping and SLNB should achieve their own learning curve and continue to perform ALND until they demonstrated proficiency with the SLNB technique (50). It is recommended that a surgeon should first learn the technique of SLNB from experienced colleagues and should perform at least 40 SLNB with ALND until false negative rate of no more than 5% is achieved before they consider using SLNB instead of ALND. The consensus

meeting held in 2002 with participation of experienced authors from United States and Europe recommended that SLNB in BC is a clinically useful procedure with high success and lower false negative rates. Furthermore, it was also noted that SLNB is not an experimental technique anymore, but a standard method of lymph node analysis for small cancers (T1a and T1b) with minimal nodal involvement and replaces unnecessary ALND in that group of patient (51).

Some new studies concerning the impact of SLNB on BC-related lymphedema have been published recently (Table 2). Schrenk et al. reported a prospective study comparing post-operative morbidity following SLNB and ALND (52). There were 35 patients in each group and all patients who underwent ALND were node negative. They assessed the preoperative and postoperative arm measurements in both groups. At an average 16 months of follow-up time, there was no significant difference in patients who underwent SLNB, whereas a significant increase in arm size was found in patients who underwent ALND. In addition a significantly higher number of patients complained of subjective lymphedema after ALND than SLNB patients who had undergone SLNB. However the short follow-up time is a limiting factor of this study. Another study done by Sener et al. reported results of 492 patients who underwent SLNB (53). In the first validation phase, 72 patients underwent an obligatory ALND after SLNB that resulted in a 6.9% of lymphedema development rate at a median 24 months of follow-up time. In that group, all patients who developed lymphedema were lymph node positive. In the second phase, patients underwent ALND, only if the SLNB was positive for tumor invasion. The lymphedema rate was 3% in patients underwent only SLNB compared with 17.1 % in lymph node positive patients who had axillary dissection subsequently. The authors concluded that lymphedema in SLNB patients might be an acute form of reactive edema, and longer follow-up time is necessary for assessment of the chronic form of the disease. Tumor location, the extent of axillary staging, and the presence of trauma and/or infection have been defined as causative factors of lymphedema development.

Giuliano et al. reported a lower complication rate of SLNB than ALND (54). In their study, the 67 SLNB negative patients did not have any further axillary surgical intervention. Fifty-seven SLNB positive patients underwent either immediate or delayed ALND. Complications were significantly increased in the ALND patients. While lymphedema was not seen in any of the patients who underwent SLNB, 6.8% (4/58) of patients underwent ALND developed lymphedema at a median follow-up time of 39 months. Temple et al. prospectively evaluated patients by measuring arm circumferences at baseline, 3, 6, 12 months after surgery (55). In contrast to Schrenk et al, they did not find any significant difference in arm circumferences between patients who underwent either SLNB or ALNB at 1 year (52, 55). Burak et al. designed a study in order to investigate SLNB and ALNB with respect to postoperative morbidity (56). They compared ipsilateral arm circumference with unaffected contralateral arm circumference in 98 patients who underwent either SLNB alone or SLNB and subsequent ALND. With a mean 15-month follow-up time, significantly increased arm circumference was observed at the mid-biceps and antecubital fossa measurements of patients who underwent ALND than in patients who underwent only SLNB. In a retrospective study Blanchard et al. evaluated 894 patients with survey letter and questionnaire (57). All patients were nodes negative, early-stage, invasive breast carcinoma. Of them 730 patients had negative SLN biopsy findings and 164 women had negative findings on SLN biopsy with ALND. Patients with axillary dissections reported a significantly higher occurrence of arm lymphedema (34%), arm pain (38%), seroma formation (24%), and infection (9%) vs SLN biopsy-only patients (6%, 14%, 7%, and 3%, respectively). Mean follow-up was 2.4 years. Schijven et al. have compared retrospectively 213 patients with ALND and 180 SLNB patients (58). Lymphedema was detected using a disease-specific quality-of-life questionnaire 1-3 years after surgery. Lymphedema reported 1.1 % in SLNB group and 7.1 in ALND group. In a retrospective study Golshan et al. reported the lymphedema rates of 77 patients who underwent SLNB and 48 patients who underwent ALND (59). Lymphedema was seen 2.6% in the SLNB group as compared with 27% in the ALND group. The minimal follow up time was one year. Recently long-term arm morbidity in node-negative BC patients with SLNB or ALND was presented in the European Cancer Conference, and authors em-

phasized that clinically appeared lymphedema was 1% in SLNB patients and 13% in ALND patients. They also reported that %2 of SLNB patients had received manual lymph drainage, but it was 15% in ALND group (P=0009).

Between 1998-2002, SLNB was performed in a total of 1,044 patients in Magee-Womens Hospital at the University of Pittsburgh. Five hundred eighty-one patients underwent SLNB plus subsequent ALND, and 461 patients underwent only SLNB. By the end of 2002, none of the patient has a complaint of lymphedema (unpublished data). These data do not reflect the actual incidence of lymphedema after SLNB at our institution until all the follow-ups are accomplished but suggests that a less aggressive surgical approach to the axilla causes less damage to lymphatic tissue if we consider 93 lymphedema cases who were diagnosed previously and, who underwent breast surgery with ALND only (61).

The time of onset of lymphedema after BC treatment varies. It sometimes appears early and, sometimes develops years later. Tengrup et al. reported that two thirds of patients presented with lymphedema during the first two years after treatment (37). Werner et al. found a 14-month mean time for development of lymphedema following BC treatment (62). They also noted that 97% of patients who ever developed arm edema did so within 4 years of treatment. However, the prevalence of lymphedema continues to increase over time. Mortimer et al. found that lymphedema prevalence was 20% at 0-2 years and 30% at 15 years after BC treatment (63).

A limited number of studies and our own experience show that SLNB seems to decrease the lymphedema rate. Although they all have relatively short periods of follow-up time, all studies agree on the effectiveness and utility of SLNB in the prevention of postoperative lymphedema, at least with short follow-up time. However, a number of different factors besides surgical trauma might play a role in the pathogenesis of lymphedema. Consequently, BC patients will continue carrying a risk for this complication. Long-term follow-up studies will yield more accurate assessment of the impact of SLNB in the prevention of breast-cancer related lymphedema.

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