

How Much Is Enough? The Continuing Debate on the Axillary Lymph Node Dissection in Breast Cancer

By Veronica C Shim, MD, FACS

Since the Halsted radical mastectomy was introduced in 1894,¹ breast cancer treatment has undergone major changes. More than a century later, breast conserving surgery is now accepted in the treatment armamentarium of early breast cancer. However, the role of axillary lymph node dissection (ALND) in breast cancer treatment continues to be controversial. The persistent question in this debate is whether we should abandon axillary lymph node evaluation in breast cancer management; I believe we cannot.

Axillary lymph node disease status is considered the most significant prognostic factor for patients with early-stage breast cancer. Surgical resection and histopathologic examination of the lymph nodes are the gold standard for evaluating the disease status of the axillary lymph node. Unfortunately, ALND is associated with lymphedema, nerve injury, shoulder dysfunction, and other morbidities that compromise quality of life in about 20% of patients.²

To lessen morbidity associated with ALND, sentinel lymph node biopsy (SLNB) was developed in the 1990s. The definition of sentinel lymph node (SLN) is the first lymph node into which cancer cells would spread from the primary tumor before involving further lymph nodes within that basin. In theory, the result of the SLNB reflects the remainder of the nodal basin for metastases. SLNB is a less invasive procedure and more accurate since it allows a pathologist to study a lymph node in greater detail. Thus, SLNB has become the standard of care in clinically node-negative patients.³⁻⁵ SLNB has also been shown to be a reliable tool after patients receive preoperative systemic treatment in locally advanced breast cancer.⁶

Currently, it is accepted that ALND is indicated when a patient presents with clinically positive axillary lymph node disease. As stated above, there is also agreement that no further ALND is indicated when the SLNB shows no disease. The major point of debate now is what to do with positive SLN in patients with other-

wise clinically negative regional disease in early breast cancer. Studies have shown that the SLN is the only positive lymph node in 38% to 67% of cases when completion ALND was followed.⁷ This reflects dramatically changed presentation over the last decade of breast cancer with decreasing primary tumor size and lymph node positivity in patients with invasive breast cancer.⁸ Unfortunately, there is no proven method other than ALND that can identify the group with additional axillary nodal disease.

There is no clear indication that ALND provides a survival benefit. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04, ALND did not show survival benefit in patients without clinical evidence of axillary adenopathy. With 25 years of follow-up, no significant survival differences have emerged.⁹ Proponents of ALND argue that B-04 did not have enough patients in the trial to see a survival benefit. A meta-analysis of six trials evaluating the impact of ALND on breast cancer survival showed an average survival benefit of 5% with ALND (95% CI=1.7-8.0%, probability of survival benefit >99.5%).¹⁰ It warrants mention that these patients received no adjuvant therapy and that tumor size was larger in these studies than the tumor size we see now. This exemplifies a common problem in evaluating the issues surrounding breast cancer treatment. The problem is that only a small benefit can be seen many years after the studies are started, and that demonstration of the benefit requires large numbers of patients as in a meta-analysis.¹¹ Thus, the data may no longer be applicable because of improved survival from other new treatment modalities.

Although ALND has not been shown to give a clear survival benefit, proponents of ALND argue that it provides better prognostic information and locoregional control. ALND can also provide additional information

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that might change the treatment course for a select few; in women with more than four positive lymph nodes, postmastectomy radiation is recommended. The importance of the number of positive axillary lymph nodes is reflected in the new American Joint Committee on Cancer staging system for breast cancer published in 2002.¹²

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More recently, in the International Breast Cancer Study Group (IBCSG) Trial 10-93, older patients (defined as those >60 years of age) who were treated with tamoxifen regardless of nodal status were randomly assigned to ALND or no surgical intervention in the axilla after either mastectomy or lumpectomy.¹³ There were no differences in disease free or overall survival, but there were only 473 patients in the study and the median follow-up was just 6.6 years. Because of poor accrual of subjects for the study, goals were amended to focus on quality of life issues. Avoidance of ALND in this trial showed similar efficacy with better early quality of life in women older than 60 years who had

clinically node-negative disease and received tamoxifen for endocrine-responsive disease. The poor accrual probably reflected the belief of many practitioners in the value of evaluating the axillary nodes even in this group of low-risk women.

The American College of Surgeons Z-11 sentinel node trial also was designed to ask the pivotal question whether ALND is necessary in patients with positive SLNB. The trial was suspended because of low accrual. Again, the failure of this trial to recruit patients reflects uncertainty by the patients and physicians about abandoning ALND in breast cancer treatment.

The most recent American Society of Clinical Oncology (ASCO) Guideline recommends SLNB in clinically node-negative patients as the initial evaluation. In patients with positive SNB, the ASCO recommends ALND.⁵ Unless and until a new prospective, randomized trial is done to readdress the issues of the therapeutic value of ALND in breast cancer, I feel that the ASCO guideline should be followed.

With the advent of molecular technology, we are moving toward an era of personalized treatment in part on the basis of genetic traits. For example, the Oncotype DX (breast cancer assay, Genomic Health, Redwood City, CA) has recently been clinically validated in the Kaiser Permanente database and is used to predict the likelihood of breast cancer recurrence in women with newly diagnosed, early stage inva-

sive cancer.¹⁴ Tests like the Oncotype DX are increasingly tailoring the breast cancer treatment to each individual patient so that we can maximize the benefit and minimize the risk of each therapy. Decisions regarding appropriate adjuvant therapy in breast cancer now increasingly involve molecular biology and genetics. Yet, a century of debate on the therapeutic value of ALND continues.

As physicians in a large, successful health maintenance organization or as physicians in a university practice, we embrace medical evidence and foster scientific research. ALND has not been shown to confer a clear survival benefit. If and when another trial comes up that asks the question of whether we should proceed to ALND in an SLNB-positive patient, each surgeon should be ready to consider enrolling his or her patients into the trial. Otherwise, we might continue to subject our patients to unnecessary morbidity without medical evidence for its benefit. At this point, however, and until this needed clinical trial becomes available, the standard of care for positive SLNB will continue to be ALND. ❖

References

1. Halsted W. The results of operations for cure of cancer of the breast performed at the Johns Hopkins Hospital from June 1889 to January 1894. *Johns Hopkins Hosp Bull* 1895;4:297.
2. Petrek J, Lerner R. Lymphedema. In: Harris JR, Lippman ME, Morrow M, Osborne CK, editors. *Diseases of the breast*. 2nd ed. Philadelphia: Lippincott, Williams & Wilkins; 2000. p 1033-9.
3. Fraile M, Rull M, Julian FJ, et al. Sentinel node biopsy as a practical alternative to axillary lymph node dissection in breast cancer patients: an approach to its validity. *Ann Oncol* 2000 Jun;11(12):701-5.
4. Miltenburg DM, Miller C, Karamlou TB, Brunicaudi FC. Meta-analysis of sentinel lymph node biopsy in breast cancer. *J Sur Res* 1999 Jun 15;84(2):138-42.
5. Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a metaanalysis. *Cancer* 2006 Jan 1;106(1):4-16.
6. Xing Y, Foy M, Cox DD, Kuerer HM, Hunt KK, Cormier JN. Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer. *Br J Surg* 2006 May;93(5):539-46.
7. Reynolds C, Mick R, Donohue JH, et al. Sentinel lymph node biopsy with metastasis: can axillary dissection be avoided in some patients with breast cancer? *J Clin Oncol* 1999 Jun;17(6):1720-6.
8. Cady B, Stone MD, Schuler JG, Thakur R, Wanner MA, Lavin PT. The new era in breast cancer: Invasion, size, and nodal involvement dramatically decreasing as a result of mammographic screening. *Arch Surg* 1996 Mar;131:301-8.
9. Fisher B, Jeong JH, Anderson S, et al. Twenty-five-year

- follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med* 2002 Aug 22;347(8):567-75.
10. Orr RK. The impact of prophylactic axillary node dissection on breast cancer survival—a Bayesian meta-analysis. *Ann Surg Oncol* 1999 Jan-Feb;6(1):109-16.
 11. Henderson IC. Axillary surgery: clinical judgment required. *J Clin Oncol* 2006 Jan 20;24(3):325-6.
 12. Singletary SE, Allred C, Ashley P, et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. *J Clin Oncol* 2002 Sep 1;20(17):3628-36.
 13. Rudenstam CM, Zahrieh D, Forbes JF, et al; International Breast Cancer Study Group. Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. *J Clin Oncol* 2006 Jan 20;24(3):337-44.
 14. Habel LA, Quesenberry CP, Jacobs M, et al. Gene expression and breast cancer mortality in Northern California Kaiser Permanente Patients: A large population-based case control study [Abstract on the Internet]. *J Clin Oncol* 2005 ASCP Annual Meeting Proceedings;23(16S): Part I of II (Jun 1 Suppl), 2005 (cited 2006 Nov 30):603. Available from: www.asco.org/portal/site/ASCPmenuitem.34d60f5624ba07fd506fe310ee37a01d?vgnextoid=76f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=abst_de tail_view &confID=34&index=y&abstractID=34009.

Pure Science

We must not forget that when radium was discovered no one knew that it would prove useful in hospitals. The work was one of pure science. And this is a proof that scientific work must not be considered from the point of view of the direct usefulness of it. It must be done for itself, for the beauty of science, and then there is always the chance that a scientific discovery may become, like the radium, a benefit for humanity.

— Marie Curie, 1867-1934, Polish chemist and early pioneer in the field of Radiology, 1903 Nobel Laureate in Physics, 1911 Nobel Laureate in Chemistry