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Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis: A Randomized Clinical Trial

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Context: Sentinel lymph node dissection (SLND) accurately identifies nodal metastasis of early breast cancer, but it is not clear whether further nodal dissection affects survival.

Objective: To determine the effects of complete axillary lymph node dissection (ALND) on survival of patients with sentinel lymph node (SLN) metastasis of breast cancer.

Design, Setting, and Patients: The American College of Surgeons Oncology Group Z0011 trial, a phase 3 noninferiority trial conducted at 115 sites and enrolling patients from May 1999 to December 2004. Patients were women with clinical T1-T2 invasive breast cancer, no palpable adenopathy, and 1 to 2 SLNs containing metastases identified by frozen section, touch preparation, or hematoxylin-eosin staining on permanent section. Targeted enrollment was 1900 women with final analysis after 500 deaths, but the trial closed early because mortality rate was lower than expected.

Interventions: All patients underwent lumpectomy and tangential whole-breast irradiation. Those with SLN metastases identified by SLND were randomized to undergo ALND or no further axillary treatment. Those randomized to ALND underwent dissection of 10 or more nodes. Systemic therapy was at the discretion of the treating physician.

Main Outcome Measures: Overall survival was the primary end point, with a noninferiority margin of a 1-sided hazard ratio of less than 1.3 indicating that SLND alone is noninferior to ALND. Disease-free survival was a secondary end point.

Results: Clinical and tumor characteristics were similar between 445 patients randomized to ALND and 446 randomized to SLND alone. However, the median number of nodes removed was 17 with ALND and 2 with SLND alone. At a median follow-up of 6.3 years (last follow-up, March 4, 2010), 5-year overall survival was 91.8% (95% confidence interval [CI], 89.1%-94.5%) with ALND and 92.5% (95% CI, 90.0%-95.1%) with SLND alone; 5-year disease-free survival was 82.2% (95% CI, 78.3%-86.3%) with ALND and 83.9% (95% CI, 80.2%-87.9%) with SLND alone. The hazard ratio for treatment-related overall survival was 0.79 (90% CI, 0.56-1.11) without adjustment and 0.87 (90% CI, 0.62-1.23) after adjusting for age and adjuvant therapy.

Conclusion: Among patients with limited SLN metastatic breast cancer treated with breast conservation and systemic therapy, the use of SLND alone compared with ALND did not result in inferior survival.

Trial Registration: clinicaltrials.gov Identifier: NCT00003855

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Less May Be Better

Axillary Dissection Is Unnecessary in Some Patients With a Positive Sentinel Lymph Node

THE RESULTS OF THE AMERICAN COLLEGE OF Surgeons Z0011 trial demonstrate that axillary lymph node dissection (ALND) does not improve survival in patients with breast cancer if limited metastatic disease is found in the sentinel lymph node (SLN). These new data are applicable to patients who present with T1 or T2 disease, have no palpable lymph nodes on physical examination, and undergo lumpectomy, SLN biopsy, and whole-breast radiotherapy followed by systemic therapy. This trial by Giuliano et al is practice changing and will lead to an improvement in the care we provide to our patients with breast cancer—ALND can be safely omitted in a subset of node-positive patients—with no impact on survival.

In 1898, Halsted presented his landmark series at the American Surgical Association of radical mastectomy in 67 patients with a 3-year survival rate of 54%. This operation remained the mainstay of surgery for more than 70 years. Although Crile, Cope, Paty, and Auschenschloss argued that the large operation was not always indicated, ultimately Fisher et al^{1,2} and Veronesi et al³ proved, via the NSABP B-04, NSABP-06, and Milan randomized controlled clinical trials, that when lesser surgeries are done (combined with irradiation therapy), there is no impact on survival. As the surgeries have become less morbid, better screening, effective chemotherapeutic regimens, endocrine therapies (such as estrogen antagonists and aromatase inhibitors), and HER2/neu antibody-directed therapy have significantly improved survival rates.

Axillary lymph node status provides prognostic information and guides adjuvant therapy. The therapeutic value of an ALND, however, has been debated for years. The morbidity of an ALND has been well documented and includes lymphedema, nerve injury, impaired range of motion, and seroma formation. Once SLN biopsy was introduced, numerous studies confirmed less morbidity when it was compared with ALND. NSABP B-32 demonstrated that when the SLN is negative, ALND did not improve survival.⁴ Since then, however, ALND remained the standard of care for lymph node–positive patients.

With the advent of SLN biopsy, smaller foci of disease were found and many times the SLN was the only site of disease. A trend developed in which not all breast surgeons would perform a completion ALND,⁵ particularly in the setting of micrometastases or isolated tumor cells in SLNs. Nomograms were created to predict the likelihood of additional disease in the non-SLNs, and breast surgeons then used this information to counsel patients on the risks and benefits of completion ALND. The Z0011 trial validates that even with lymph node metastases, ALND will be unnecessary in some patients.

According to Giuliano et al, ALND in the select group of woman studied only increases the number of positive lymph nodes harvested; it had no effect on disease-free interval, local control, or overall survival. To be specific, in this trial, 891 women with T1 or T2 breast cancer with a clinically negative axilla undergoing breast conservation surgery with 1 or 2 positive SLNs were randomized to SLN biopsy alone or SLN biopsy with ALND. All received tangential whole-breast irradiation, and more than 90% received adjuvant systemic therapy. Third-field nodal irradiation was specifically not allowed. Patients with 3 or more positive SLNs and patients with gross extranodal disease were ineligible.

The trial did not achieve its target accrual and was closed early because of low mortality rates. The expected survival rate when the trial was conceived in 1999 was 80% at 5 years, but the observed 5-year survival rate in the current study, in which all had positive SLNs, was more than 90%. Specifically, it was 91.8% for those who underwent with ALND and 92.5% for those who underwent SLN biopsy alone. Furthermore, the 5-year disease-free survival was 82.2% with ALND and 83.9% with SLN biopsy alone. Although only 981 of the planned 1900 patients were enrolled, the hypothesis that SNL biopsy is “noninferior” to ALND in this subset of patients was proved.

Many surgeons were reluctant to participate in this trial because of their preconceived bias that the patients in the SLN biopsy alone group would surely do poorly without additional axillary therapy. The low accrual rate and lack of follow-up more than 5 years should raise some concern about long-term conclusions. In the ALND group, the study found that 72.3% of the women had all of their disease removed by the SLN biopsy. Therefore, there was only a potential benefit of an ANLD to the 27% of the population with non-SLN metastases, or 240 patients. Is this enough patients to conclude there is no benefit, especially when 18% of these patients were lost to follow-up? Also, while many local recurrences occur in the first

5 years, the risk of local recurrence continues over time, especially in the hormone receptor–positive patients. What will happen once their endocrine therapies are stopped? Will we see late recurrences, and if so, will it affect survival? Or will delayed ALND at that time suffice much like that seen in NSABP-04?

Furthermore, while all of the patients in this trial received tangential whole-breast radiotherapy, the amount of irradiation to the low axilla was not quantified. Some prior studies have demonstrated that standard breast tangents can frequently irradiate the area of the SLN.⁶ How much does irradiation really contribute to control of disease? Additional studies addressing the role of irradiation therapy are pending, including the AMAROS trial, a randomized European trial that is comparing completion ALND with axillary irradiation in patients with early-stage breast cancer with a positive SLN. Keep in mind, however, that specific third-field axillary nodal irradiation may be associated with a risk of lymphedema and was not needed or even allowed in the Z0011 trial.

Given the small number of adverse events, it may not be possible to detect differences in the 2 population groups until well after 5 years. Many patients in the study had no residual disease after SLN excision, and in those with residual disease, the volume should be low enough that it can be adequately treated with adjuvant systemic therapy and whole-breast irradiation. While most women who fit the criteria of this patient population will not develop a recurrence, those few individuals who do have a recurrence may ultimately do poorly. As a result, each individual patient should be carefully evaluated to determine risks and benefits of the procedure and how it will affect her multidisciplinary care.

Nonetheless, this is a landmark study. It should change the practice of surgery for patients with T1 or T2 disease with clinically negative axillae and limited disease in their SLN who choose breast conservation therapy. They do not need ALND. In fact, there may be a time that even SLN biopsy is obsolete in select patients given that systemic treatment is often decided by the features of the tumor itself, such as hormone receptor status, HER2/neu amplifications, and multigene expression assays regardless of the lymph node status.

This new approach is not applicable to all patients, specifically those undergoing mastectomy or lumpectomy without whole-breast irradiation or those treated with neoadjuvant therapy. It also does not apply to those patients who present with clinically positive lymph nodes or in those patients who do not plan to undergo standard systemic treatment. For now, most of these patients with positive lymph nodes should still have ALND. Their care should be individualized with thoughtful discussions between the patient, the surgeon, and the rest of the multidisciplinary team regarding the risks and benefits of ALND as well as the role of potential adjuvant therapies. Further studies are needed to determine which of these patients clearly need ALND.

We have come a long way from the landmark study of Halsted, and we have a long way to go. Giuliano et al should be commended for having the foresight to institute and execute this trial. As additional studies come about to answer the many questions raised by this trial,

the importance of entering our patients into these clinical trials cannot be overstressed.

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