

Positive sentinel lymph nodes should be followed by axillary lymph node dissection

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Abstract The use of sentinel lymph node biopsy (SLNB) has revolutionized breast surgery for early stage breast cancer. SLNB accurately stages the axilla without the morbidity of axillary lymph node dissection (ALND). While allowing those patients with No disease to avoid a potentially morbid dissection, SLNB is a diagnostic procedure which identifies nodal disease and is not designed to replace ALND in patients with metastatic disease in the axilla. ALND provides regional disease control, assists physicians in making decisions for patients regarding systemic therapy, and may or may not have a survival advantage. The American College of Surgeons Oncology Group Z0011 study was constructed to determine whether there was a survival difference between completion ALND vs. observation in patients with a positive sentinel lymph node (SLN). Without strong data from randomized, controlled trials regarding the locoregional and long-term survival of patients who undergo observation after a positive SLN, patients should be offered completion ALND for a positive SLNB although ALND may offer no survival advantage.

Keywords: Axillary lymph node dissection; Breast cancer; Sentinel lymph node dissection

Introduction

Fisher *et al.* in the NSABP B-04 study demonstrated that mastectomy and ALND or mastectomy and radiation to the axilla improved regional control, but did not influence survival compared to total mastectomy [1]. The authors postulated that breast cancer was a systemic disease at inception and variation in locoregional therapy would not alter survival. This concept affected the entire philosophy of managing breast cancer and became an important part of the foundation for breast conserving surgery for early breast cancer. Sentinel lymph node biopsy (SLNB) continued the evolution in breast cancer surgery. SLNB is a less morbid method to stage the axilla when compared to axillary lymph node dissection (ALND) [2].

The sentinel lymph node (SLN) has been shown to accurately represent the presence of metastatic disease in the axilla, and therefore, node-negative patients may be spared the morbidity of an ALND [3–6]. However, those patients with a positive SLN have traditionally undergone a completion ALND. This decision has been recently been challenged in several retrospective studies and case reports [7,8]. The purpose of the SLNB is to establish stage, but is not necessarily therapeutic. ALND can offer important prognostic staging information, control regional disease, and may or may not confer a survival advantage to patients with axillary metastasis.

Staging and prognosis

SLNB research in breast cancer began in 1991 and Giuliano reported 174 cases of SLNB followed by ALND to determine staging accuracy. SLNB has been validated as an accurate method to stage the clinically negative axilla [9]. Veronesi *et al.* performed

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SLNB in 373 patients who subsequently were observed only if their SLN was negative. In those patients who had a positive SLN, they were treated with an ALND. None of the patients with a negative SLN recurred [10]. An additional study followed 953 patients with a negative SLN over 5 years. There was a 0.3% rate of ipsilateral metastasis at follow-up demonstrating that a negative SLN is predictive for a negative axillary nodal basin [11]. In a trial of 516 patients with tumors 2 cm or less, patients were randomized to SLNB and ALND vs. SLNB and ALND only if the SLN was positive. The accuracy of SLNB was 96.9% with only 4.6% of all patients with a negative SLN harboring axillary metastases in non-SLN [3]. These findings also have been validated in additional studies [12,13]. Current American Society of Clinical Oncology (ASCO) guidelines allow SNLB for patients with a primary tumor less than 5 cm in size with a clinically negative axilla. These guidelines suggest that those patients with a macrometastatic (>2 mm) or a micrometastatic (>0.2, < or equal to 2 mm) tumor deposit in the SLN should undergo an ALND to eliminate any additional nodal disease [14].

SLNB more importantly predicts the presence of additional nodal disease. The John Wayne Cancer Institute reported results of 156 patients who had a completion ALND after a positive SLN. Thirty-five percent of patients with a positive SLN had additional nodal disease discovered after a completion ALND. The presence of positive non-SLN correlated with larger tumor size (> or equal to 2 cm) and the size of the SLN metastatic deposit. Less than 10% of patients had non-SLN metastasis with SLN micrometastatic disease [15]. Menes *et al.* also demonstrated that patients with SLN metastasis up to 2 mm in diameter had a 46% rate of additional non-SLN metastasis [16]. Therefore, additional significant disease may remain in the axilla after a positive sentinel lymph node.

The prognostic information garnered from the ALND is valuable in determining whether a patient with extensive nodal disease would benefit from additional therapy. Tumor characteristics such as estrogen/progesterone status are important to determine the aggressiveness of a particular tumor; however, the most important prognostic factor remains lymph node status [17]. In addition to establishing the extent of tumor burden, patients with multiple lymph nodes are candidates for additional treatment which would otherwise not be offered to them. Patients with more than ten lymph nodes were historically considered candidates for bone marrow transplants and intensive chemotherapy, but these treatments were abandoned after finding no survival benefit [18]. Third field axillary radiation is usually recommended to patients with more than four positive lymph nodes. Some authors advocate post-mastectomy radiation to clear

potentially positive lymph nodes. Overgaard *et al.* and Ragaz *et al.* both noted that the improvement of disease-free survival and overall survival when radiation was given post-operatively, particularly as the number of positive lymph nodes increased [19,20].

Regional recurrence

Regional control after breast conserving therapy is dependent upon removing all possible disease from the axilla. Omitting ALND in patients with a positive SLN may leave residual disease in up to 50% of patients which could impact axillary recurrence rates [15]. Radiation is currently being evaluated in clinical trials for positive SLN and in patients who decline ALND after a positive SLN. The Early Breast Cancer Trialists' Collaborative Group completed a meta-analysis of randomized trials regarding radiation and early breast cancer. They compared eight trials of radiation vs. surgery and were unable to find a statistically significant difference in mortality, but they did find a decrease in locoregional recurrence after surgery with radiation. However, the results of such an analysis must reflect the inherent flaws of a meta-analysis. Many of the trials included in the analysis had additional treatments ranging from tamoxifen to ovarian ablation. Therefore, it is unable to conclude with any certainty that radiation has any benefit over ALND since each will decrease regional recurrence [21].

In contrast, the Institute Curie designed a study randomizing 658 women with less than 3 cm tumors with clinically negative lymph nodes, to either ALND or radiotherapy. Twenty-one percent of women undergoing ALND had positive lymph nodes. At a follow-up of 18 months, they found no overall survival benefit, but the rate of axillary recurrence without a concomitant in-breast recurrent was higher in those patients undergoing only radiation therapy (1% ALND vs. 3% radiation) [22]. In the Scottish trial, surgical approaches to the axilla included either 'axillary sampling' or ALND. Radiation therapy was then applied to both groups. The authors demonstrated that radiation increased the percentage of patients free from recurrence or death. More importantly, those patients with ALND had a greater local control than those who underwent 'sampling' [23]. Both radiation and ALND improve regional control.

Overall survival

Regional axillary control may affect the patient's ultimate survival. The Guy's Hospital trial study randomized patients to either wide local excision (WLE) without ALND or mastectomy with ALND. Both groups received what is now recognized to be low-dose post-operative radiation. The difference between

the two groups may hinge on the ALND which accompanied the mastectomy group. The authors found a survival benefit in those patients who underwent a mastectomy with ALND [24]. At 25 years of follow-up, there was still a difference in relapse rate (25% mastectomy vs. 50% with WLE). There was also a corresponding increase in breast cancer deaths with WLE (57% mastectomy vs. 44% WLE, $P = 0.04$) [25].

The Danish Breast Cancer Cooperative Group also demonstrated that in both high-risk pre- and post-menopausal women with breast cancer, post-operative radiation therapy improved disease-free and overall survival when compared to tamoxifen alone. The relative improvement in survival was more pronounced as the number of positive lymph nodes increased [19,26]. Shuka *et al.* described 457 patients randomized to simple mastectomy without ALND vs. a Halstead radical mastectomy which included ALND. Patients with the ALND had a decrease in systemic recurrence, 43.3% with Halstead mastectomy vs. 59.7% with simple mastectomy, and an overall survival advantage of 16.2%. The decrease in recurrence was more pronounced in patients with 1–3 positive lymph nodes [27]. While, Halstead mastectomy is rarely performed in the United States today, the implication from the prospective study is that removal of lymph nodes may affect the systemic spread of disease and improve survival.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial suggests that ALND has a prognostic, but not a therapeutic role in the treatment of early breast cancer. The trial randomized 1765 women to either Halstead radical mastectomy, total mastectomy without ALND, but with radiation, or total mastectomy without ALND or radiation. None of the participants received adjuvant therapy. The authors found no difference in disease-free survival or overall survival between the three groups despite the fact that approximately 40% of patients were estimated to have untreated metastatic disease in the axilla [28]. There are several design flaws however, which may bias the results. The sample size was too small to exclude a small survival advantage and 35% of women in the radical mastectomy group had an inadequate ALND. Orr conducted a meta-analysis of several randomized trials, including B-04, comparing mastectomy/ALND or segmentectomy/ALND to those with mastectomy or segmentectomy alone. There was an overall 5.4% survival advantage for clinically node-negative patients who were treated with ALND. In particular, re-analysis of B-04 demonstrated a 1% survival benefit for ALND at 5 year follow-up and 4% at 10 year follow-up. Therefore, if B-04 had been calculated for a larger sample size, the probability of a survival advantage at 10 years is 86% [29]. However, at 25 year follow-up, no survival advantage was demonstrated.

Conclusions

ALND has several disadvantages such as increased risk of lymphedema and posterior arm sensory changes, making SLNB a preferred method to determine axillary status. There are several questions still remaining regarding the application of ALND, in particular with SLN micrometastasis and isolated tumor cells. The American College of Surgeon's Oncology Group (ACOSOG) Z0011 trial hoped to determine whether ALND following positive SLNB altered survival and local control in patients with a positive SLN [30]. This study has been closed with approximately 900 patients because of low event rates and poor accrual. Data from Z0011 may still assist in determining the final role of ALND.

Sentinel lymph node dissection has a role in establishing staging of patients and determining prognosis. Several characteristics including primary tumor size and lymphovascular invasion can determine the likelihood of residual metastatic disease, but the most important is the size of the metastasis in the sentinel lymph node. Previous studies comparing primary surgical treatment with or without ALND have demonstrated no survival advantage, but were significantly underpowered. Larger sample sizes in studies such as ACOSOG Z0011 which specifically address axillary treatment could have determined the role of ALND, but until such data is available, ALND remains the standard of care for patients with a positive SLN.

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