Point–Counterpoint Review

Cancer Research

Point

It Is Not Always Necessary to Do Axillary Dissection for T1 and T2 Breast Cancer

See Counterpoint and Reply by Sabel, p. 7156 and p. 7155

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Abstract

Axillary lymph node dissection (ALND) has been a part of breast cancer management since the 1900s. The idea that axillary metastases do not require surgical removal is a repudiation of the Halstedian concept of breast cancer biology, yet multiple prospective randomized studies show that the incidence of nodal recurrence in patients not having ALND is substantially lower than expected, based on the incidence of axillary metastases in patients having ALND, and survival does not differ based on axillary treatment. Avoidance of axillary dissection significantly reduces the morbidity of breast cancer surgery. As the use of systemic therapy has increased and targeted therapies have become available, the incidence of axillary recurrence in patients not having dissection has decreased to approximately 1% at 5 years, making routine axillary dissection difficult to justify. ALND is no longer standard management for patients with T1 and T2, clinically node-negative cancers undergoing breast-conserving therapy and found to have a positive sentinel node, and can also be avoided in patients with these tumor features having mastectomy if the need for postmastectomy radiotherapy is clear with the finding of a positive sentinel node. *Cancer Res; 73(24); 7151–4. ©2013 AACR.*

For many years, axillary lymph node dissection (ALND) was a standard part of the management of invasive breast cancer. ALND effectively identified nodal metastases and maintained local control in the axilla, although its contribution to breast cancer survival was uncertain (1). More recently, sentinel node biopsy has replaced ALND as the staging procedure of choice for women with T1 and T2 breast cancer. A sentinel lymph node can be identified in more that 95% of women with early-stage breast cancer (2, 3) and predicts the status of the remaining axillary nodes with more than 90% accuracy (3, 4). Staging with sentinel node biopsy was not associated with any decrease in survival compared with ALND in randomized trials (3, 4), and the procedure is now widely accepted as the standard approach to staging the clinically negative axilla. An important lesson learned from the initial experience with the sentinel node technique was that the clinical incidence of axillary recurrence was significantly lower than the false-negative rate of sentinel node biopsy in studies where completion ALND was done. Despite false-negative rates of 10% to 15% in prospective, multicenter trials (3, 5, 6), in a meta-analysis of 48 studies, including 14,959 sentinel node-negative patients, axillary failure was seen in only 0.3% after a median follow-up of 34 months (7). The fact that all residual axillary disease in the setting of a negative sentinel node does not become clinically evident as local recurrence, nor does it have a negative survival impact, is well accepted, but the implications of these findings for the management of patients found to have metastases in the sentinel node are often overlooked.

The major controversy today is whether all patients with sentinel node metastases require ALND. The therapeutic benefit of ALND was first addressed more than 30 years ago in the prospective, randomized National Surgical Adjuvant Breast and Bowel Project (NSABP) B04 trial, in which clinically node-negative women were randomized to radical mastectomy (removal of the breast, pectoral muscles, and axillary nodes), removal of the breast (total mastectomy) with irradiation of the draining lymph nodes, or total mastectomy only with delayed ALND if clinically evident nodal disease occurred. After 25 years of follow-up, no survival differences among the groups were seen and only 18.5% of patients in the axillary observation arm developed axillary recurrence, despite the finding of axillary nodal metastases in 40% of those undergoing ALND (8). This is particularly noteworthy because this study antedated the use of adjuvant systemic therapy. The findings of NSABP B04 did not lead to abandonment of ALND, in part because nodal status was initially used to select patients for adjuvant systemic therapy and, in part, because the 18.5% incidence of axillary recurrence was thought to be unacceptably high.

The NSABP B04 study was conducted before the widespread adoption of screening mammography, and the tumors seen today are smaller, with a correspondingly lower nodal disease burden. In a meta-analysis of 8,059 patients in 69 studies of

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sentinel node biopsy carried out, between 1970 and 2003, in patients with metastases to the sentinel node, additional nodal metastases were present in only 48% [95% confidence interval (CI), 35%–62%] of patients (9). In addition, it is now apparent that the adjuvant systemic therapy that is a routine part of the management of women with axillary nodal metastases significantly reduces locoregional recurrence (10). In the NSABP B14 trial comparing treatment with tamoxifen or placebo in estrogen receptor (ER)-positive women, the use of tamoxifen reduced the locoregional recurrence rate from 14.7% to 4.3% (11). A similar benefit was seen when chemotherapy was compared with placebo in ER-negative women in the NSABP B13 trial, with locoregional recurrence reduced from 13.4% to 2.6% (12). As systemic outcomes improve, a parallel improvement in local control is observed. This was illustrated in the NSABP B31 trial examining the addition of trastuzumab to chemotherapy in women with HER2-overexpressing cancers (13). The addition of trastuzumab resulted in both a statistically significant improvement in disease-free survival and a 40% reduction in locoregional recurrence compared with treatment with chemotherapy alone. The combination of a lower axillary nodal disease burden in node-positive women, and the widespread use of systemic therapy, even for small node-negative breast cancers, coupled with the increasing use of biologic features of the tumor rather than number of lymph nodes containing metastases to select systemic therapy, led to several recently reported, prospective, randomized trials reexamining the need for ALND in patients with sentinel node metastases. The first of these studies, the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial, randomized clinically node-negative women with T1 and T2 breast cancer and sentinel node metastases detected by routine hematoxylin and eosin staining to completion ALND or no further axillary treatment. The planned accrual was 1,900; the study closed with 891 patients due to slow accrual and a low event rate (14). At a median follow-up of 6.3 years, no differences in disease-free or overall survival were seen between groups. The rate of regional recurrence after sentinel node biopsy only was 0.9%, despite the finding of additional positive nodes in 27.4% of patients having ALND (where the regional recurrence rate was 0.5%; $P = 0.45$ vs. sentinel node only). Using the predefined statistical analysis plan, noninferiority of sentinel node biopsy was shown with a P value of 0.008. Both early postoperative complications and late morbidity, such as lymphedema and paresthesias, were significantly lower in patients undergoing sentinel node biopsy only (15). It has been suggested that patients in this study were not representative of patients with breast cancer as a whole, but were a highly selected, favorable subgroup. Investigators from Memorial Sloan-Kettering Cancer Center (16) prospectively applied the ACOSOG Z0011 eligibility criteria to an unselected, consecutive series of women with T1 and T2, clinically node-negative breast cancer undergoing breast-conserving surgery with whole-breast irradiation. Criteria for ALND, as in ACOSOG Z0011, were metastases to $\geq$3 sentinel nodes or the finding of matted nodes intraoperatively. Of 287 consecutive patients, 242 (84%) were appropriate for management without ALND, and age, hormone receptor status, and HER2 overexpression were not predictors of the need for ALND. Patient age, tumor size, and receptor status were very similar to those seen in the ACOSOG Z0011 patients, suggesting that trial participants were more representative of patients undergoing breast-conserving surgery than was initially thought and that ALND, and its associated morbidity, can be avoided in the majority of women.

Other randomized trials support these findings. The International Breast Cancer Study Group (IBCSG) 23-01 trial randomized 934 patients with micrometastases in the sentinel node to ALND or sentinel node biopsy alone. After a median follow-up of 5 years, regional recurrence was seen in 1% of the sentinel node group versus 0.2% of the ALND group, and no statistically significant differences in disease-free survival were noted in spite of the fact that 13% of patients in the ALND arm had additional nodal metastases (17). Table 1 summarizes a series of prospective, randomized trials that illustrate several key points relevant to axillary management: first, regardless of the patient population studied, the rate of axillary recurrence in patients not undergoing ALND is substantially lower than would be expected on the basis of the incidence of nodal metastases in those having ALND; and second, that as the use of whole-breast irradiation and systemic therapy increases, the likelihood of axillary failure decreases. In the NSABP B04 study (8), where no radiotherapy and no systemic therapy were given,

Table 1. Trials of axillary dissection versus less surgery

Trial	% RT	% Systemic therapy	Additional positive nodes at ALND (%)	Axillary recurrence, no ALND (%)	Ratio axillary recurrence to positive nodes
NSABP B04	0	0	40	18.5	2.2
NSABP B32	82	84	9.8	0.7	14
IBCSG 23-01	71[a]	96	13.0	1.0	13
ACOSOG Z0011	89	97	27.4	0.9	30

NOTE: NSABP, National Surgical Adjuvant Breast and Bowel Project; IBCSG, International Breast Study Group; ACOSOG, American College of Surgeons Oncology Group; RT, radiation therapy; ALND, axillary lymph node dissection.
[a]Excludes intraoperative radiotherapy.

one axillary recurrence for every 2.2 patients with disease left in the axilla was observed. In contrast, in both the NSABP B32 (3) and IBCSG 23-01 (17) studies, this ratio increased to one recurrence per 13 or 14 patients with residual nodal disease in the setting of chemotherapy and radiotherapy use in more than 70% of patients. Further reductions in regional recurrence were seen in the ACOSOG Z0011 trial (14), where a greater proportion of patients received both radiotherapy and systemic therapy. In none of these studies was more extensive axillary surgery associated with a survival benefit, emphasizing that, in the era of effective multimodality therapy, surgical removal of all microscopic disease in the breast or axillary nodes is not necessary. The lack of a survival benefit for ALND is consistent with the increasing recognition of the importance of tumor biology, rather than traditional anatomic prognostic factors of tumor size and nodal metastases, in determining patient outcomes and is supported by mathematical models of breast cancer dissemination (18).

Further support for the concept that ALND is not necessary for all patients with sentinel node metastases comes from the After Mapping of the Axilla Radiotherapy or Surgery (AMAROS) trial, a study comparing axillary recurrence rates in 1,425 sentinel node positive patients having breast-conserving surgery or mastectomy, and randomized to ALND or radiotherapy to the axillary and supraclavicular nodes. The axillary recurrence rates were 0.43% after ALND and 1.19% after radiotherapy, in spite of the finding that 32.8% of patients having ALND had additional positive nodes (19). Disease-free survival after ALND was not significantly improved (HR, 1.18; 95% CI, 0.93–1.15), and the incidence of lymphedema at 5 years was significantly lower in patients receiving radiotherapy (14% vs. 22%, $P < 0.0001$). The AMAROS study, which included patients undergoing mastectomy, who were excluded from the ACOSOG Z0011 trial (14), suggests that in patients in whom it is clear that postmastectomy radiotherapy is indicated on the basis of primary tumor characteristics and the finding of a positive sentinel node, ALND can be avoided. However, for patients having breast conservation, it is not certain that the node fields require radiotherapy. The patient populations in the ACOSOG Z0011 (14) and the AMAROS (19) trials were similar, and excellent results were obtained in the ACOSOG Z0011 trial with only treatment of breast tangents. This remains a subject for further study.

In summary, multiple prospective, randomized trials indicate that high rates of local control in the axilla are achieved without surgical removal of all microscopic disease, significantly reducing the morbidity of treatment for patients. ALND should no longer be considered standard management for clinically node-negative patients with T1 and T2 breast cancer undergoing breast-conserving surgery who will receive whole-breast irradiation. Initial information from the AMAROS trial suggests that patients with these characteristics undergoing mastectomy who will receive postmastectomy irradiation also do not require ALND. ALND remains the standard management for patients presenting with clinically evident nodal disease (after a confirmatory biopsy), those with locally advanced breast cancer, and patients having mastectomy where knowledge of the total number of involved nodes is important in determining the need for postmastectomy radiotherapy. As the effectiveness of the systemic therapy used to improve breast cancer survival continues to increase, we must continue to ask whether corresponding improvements in local control, which might allow decreasing of the extent of local therapy, also occur. The selective use of ALND represents a first step in this process. If we do not do this, we will lose an important opportunity to decrease the morbidity of treatment.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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