Role of axillary lymph-node dissection in the management of breast cancer

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In this issue of the journal, Marschall and colleagues[1] reassess the role of axillary lymph-node dissection (ALND) in the management of early-stage breast cancer. Although they mention the multiple facets of this issue in their introduction and discussion sections, their review really addresses only 1 aspect of the potential role of axillary dissection: whether ALND is necessary to identify patients who are at high risk for recurrence and therefore merit adjuvant chemotherapy. They suggest that other criteria indicative of high risk can be garnered by analysis of the tumour alone, criteria such as nuclear grade, estrogen-receptor status, lymphovascular invasion and tumour size. They use 2 different clinical practice guidelines to stratify patients for risk of recurrence regardless of nodal status. Both of these (one from Canada, the other from the United States National Institutes of Health [NIH]) are consensus guidelines only and differ considerably in their criteria for management: 15% more patients are assigned chemotherapy using NIH criteria; among patients 70 years of age or older, the percentage of women requiring ALND to guide management was 57.8 using Canadian criteria and 30.2 using NIH criteria. Other such guidelines exist,[2] which also differ in classification and recommended management. None have ever been subjected to scientific validation. Questions related to differing definitions of ER positivity and poor nuclear grade (include or exclude grade II) also arise.

The commonest initial site of tumour spread in breast cancer is to axillary nodes. The incidence of axillary involvement at the time of diagnosis correlates with many characteristics of the primary tumour, including tumour size and clinical stage. Although incidence correlates directly with the size of the primary tumour, even among occult tumours 1 cm or smaller, up to 20% will be associated with axillary lymph-node metastasis. Clinical stage is also an indicator of the likelihood of axillary metastasis, yet even in clinical stage I (clinically uninvolved axillary nodes), the rate of axillary metastasis ranges from 20%–40%, with a mean false-negative rate (clinically negative but pathologically positive) of 30%. In patients with clinical stage II tumours, up to 40% (mean 35%) will have uninvolved nodes.[3,4] Thus, in approximately one-third of cases, clinical assessment of axillary lymph-node status, and thus clinical stage, is incorrect. As Danforth[3] has emphasized, one of the reasons to perform ALND is to accurately stage the tumour. Such information is essential in determining patient eligibility for prospective randomized clinical trials. Most clinical practice guidelines are applied to patients in whom the true status of the axillary nodes is known. Nowhere in their study do Marschall and colleagues mention the clinical stage of their patients. All patients were pathological stage I or II.

Of patients with involvement of the lymph nodes, 20%–30% will have metastatic disease to level II or III (rarely), often with level I nodes being negative. With increasing numbers of involved lymph nodes, overall survival and disease-free survival at 5 and 10 years become progressively worse. Fisher and associates[5] have shown that when 10 or fewer nodes are removed and examined, 11% will have 4 or more nodes involved; when 25 or more nodes are examined, 24% will have 4 or more nodes involved. Subgroups are characteristically analyzed according to 0, 1–3, 4–9 and 10 or more involved nodes, patients in the last group often being chosen for more radical adjuvant interventions such as bone marrow transplantation because of the dismal prognosis. The number of axillary metastatic nodes also correlates with local regional recurrence after radical surgery. In the absence of positive nodes, the recurrence rate in the operative field ranges from 0%–11%. The local recurrence rate increases to 40%–50% among patients with 4 or more involved nodes.

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These local regional recurrences are primarily in the chest-wall, parasternal or supraclavicular regions.[3] This information is of value in selecting the use of postoperative radiotherapy and its fields of application. All of these data support the recommendation for dissection of a minimum of levels I and II of the axilla.

The rate of recurrence in the axilla is determined by the presence or absence of positive nodes, the stage of the cancer and the extent of axillary dissection. With complete axillary dissection the recurrence rate is less than 5%. Axillary recurrence among patients with clinically negative nodes who do not undergo axillary dissection (total mastectomy only) averages 20%–25%.[3,4] This is considerable even if all these tumours are resectable at the time of clinical detection, and patient survival is unaffected.[6] In the present series, almost 40% of women younger than 70 years would not have received ALND but had positive nodes, another important reason for performing ALND in patients with clinical stage I tumours in addition to obtaining prognostic information (i.e., to achieve local control).

Patients with clinically positive axillary nodes (clinical stage II) should have a complete ALND, including all 3 axillary levels for the following reasons, as cited by Danforth[3] in his comprehensive review. This effectively controls local disease and usually eliminates the need to treat the partially dissected axilla with postoperative radiotherapy, which can increase subsequent morbidity, especially breast and arm edema. Simple mastectomy alone in clinical stage II, leaving the axilla intact, results in a progressive axillary disease rate of 50%, which can lead to a situation in which the disease is inoperable. Whereas the majority of patients now receive adjuvant chemotherapy or hormonotherapy, or both, based on criteria other than the clinically positive lymph nodes, as Marschall and colleagues have demonstrated, axillary dissection should still be considered standard therapy. We have no evidence that systemic therapy alone is effective for these purposes. In the National Surgical Adjuvant Breast Project (NSABP) B06 trial[7] the breast recurrence rate in patients having positive nodes with partial mastectomy and systemic chemotherapy only was 44.2%. Therefore, one should probably not rely on systemic treatment alone to control axillary disease despite the increasing efficacy and potency of present chemotherapy. Second, the presence and number of positive nodes may influence the decision between hormonotherapy or chemotherapy, or both, and the choice of drugs.

Postoperative complications of ALND include seroma, wound infection, decreased shoulder mobility, nerve injury, breast edema (with breast preservation) and arm edema. Much of our information on incidence of complications has come from studies that included radical or modified radical mastectomy. It is noteworthy that in the present series, despite the worldwide movement to conservative breast surgery and the authors advocating abandonment of axillary dissection, modified radical mastectomy was done in 50% of the patients! Seroma, the commonest complication, is self-limited and usually resolves in 2 weeks. Nerve injury is extremely rare in the hands of experienced breast surgeons. Preservation of the intercostobrachial nerve, if not involved with tumour, will reduce postoperative dysesthesias of the arm. A program of gradual but immediate shoulder mobilization postoperatively allows excellent return of function. Breast edema is more often related to local radiotherapy but is compounded by ALND.

The increased scrutiny given to axillary dissection derives in part from the lack of an effective treatment for chronic lymphedema. The risk of early arm edema correlates with the extent of surgery, ranging from 35% to 40% for full dissection and 5% to 10% for lower dissection. Radiation is the most important factor that, when combined with axillary dissection, results in significant arm edema. For this reason, we should make every effort to ensure that the axilla is not included in the radiation field after a complete axillary dissection. Full dissection and radiation are associated with an unacceptably high risk. With limitation of the axillary dissection to levels I and II, the occurrence rate of chronic lymphedema has decreased to 5%. ALND is well tolerated and can be performed with a low incidence of complications.[3]

Lymphatic mapping and sentinel lymph node (SLN) biopsy initially developed by Morton and colleagues[8] at John Wayne Cancer Institute in Santa Monica, Calif., for the treatment of malignant melanoma has recently been applied to breast cancer lymph-node evaluation. These new techniques accurately provide crucial staging information while inflicting far less morbidity than complete axillary dissection. Research has suggested that the sentinel nodes (the first node[s] that receive efferent lymphatic flow from a tumour) can be identified by a gamma detector probe intraoperatively[9] using technetium-99m-labelled sulfur colloid injected around the tumour site 1–2 hours preoperatively, and by staining with Lymphazurin Blue Dye (United States Surgical) injected intraoperatively.[10] The SLN hypothesis is that malignant cells shed from the tumour will travel this same pathway, thus the SLN will be the most likely site of metastatic nodal disease if it exists.

Bass and associates[11] were able to identify an SLN in 95% of 700 patients; 26% had a positive SLN. Of 186 patients who underwent a complete axillary dissection after SLN biopsy, the false-negative rate was 0.83%. Similar excellent results have been reported by Guiliano and associates[12] among others. Initial experience with lymphatic mapping has

demonstrated that this technique not only lowers surgical morbidity and is more cost-effective but may actually be a superior tool in staging the axilla, permitting a more focused and intensive examination of the few lymph node(s) most likely to harbour metastases. By providing only 1 or 2 SLNs, the pathologist can devote more time and resources to detailed examination with serial sectioning, cytokeratin immunohistochemical (IHC) staining and the reverse transcriptase-polymerase chain reaction (RT-PCR) compared with traditional single section staining with hematoxylin–eosin for each of many nodes.[13] This allows detection of micrometastasis in more than 10% of patients than when all nodes are removed. The Ludwig Breast Cancer Study Group[14] has shown decreased survival in patients with micrometastasis, but the results are still preliminary and inconclusive with respect to the significance of cytokeratin IHC micrometastasis.[13]

A number of potential paradigm-shifting prospective randomized studies are underway.[15] The NSABP B32, a phase 3 clinical trial compares SLN dissection to conventional axillary dissection in women with breast cancer who are clinically node negative (Fig. 1). In this trial, surgeons will localize and remove only 1 (or a few) SLN by simple biopsy to determine if the node is pathologically positive or negative for cancer. What the impact of removing only SLNs will have on cancer control and survival is entirely unknown. The NSABP B32 is designed to determine if only SLN resection in breast cancer patients who are clinically node negative and pathologically SLN negative will provide the same prognostic information, regional control and disease-free and overall survival as conventional axillary dissection while significantly reducing morbidity. A secondary aim includes determining if the more detailed pathological investigation of the sentinel node will identify a group of patients with a potentially increased risk of systemic recurrence.

The American College of Surgeons Oncology Group has 2 ongoing trials. Trial Z0010 is investigating the prevalence and prognostic significance of SLN and bone-marrow micrometastasis in women with clinical T1 or T2 N0M0 breast cancer (5300 patients, study now closed). Hematoxylin–eosin-negative but immunoreactive SLN patients will be observed to determine prognostic significance. Z0011 is a randomized trial of ALND in similar clinical stage patients who have a positive SLN (by hematoxylin–eosin staining). Half will undergo a completion axillary dissection and half will have observation only.

The current standard of care for managing invasive breast cancer remains complete removal of the tumour by either mastectomy or lumpectomy and documentation of uninvolved margins followed by complete levels I–II ALND. To disregard this surgical staging (the most important validated prognostic factor), combined with the use of adjuvant chemotherapy in all or almost all patients based on unvalidated and differing clinical practice guidelines may result in greater long-term morbidity (e.g., leukemia, heart failure) to the entire population of patients.[11] According to NIH guidelines, all patients with tumours greater than 1 cm are considered high risk. This was 82.5% of patients 70 years of age or younger in the series of Marschall and colleagues. Lymphatic mapping and SLN evaluation is clearly challenging this standard treatment and providing effective tools to define more efficiently subsets of patients,

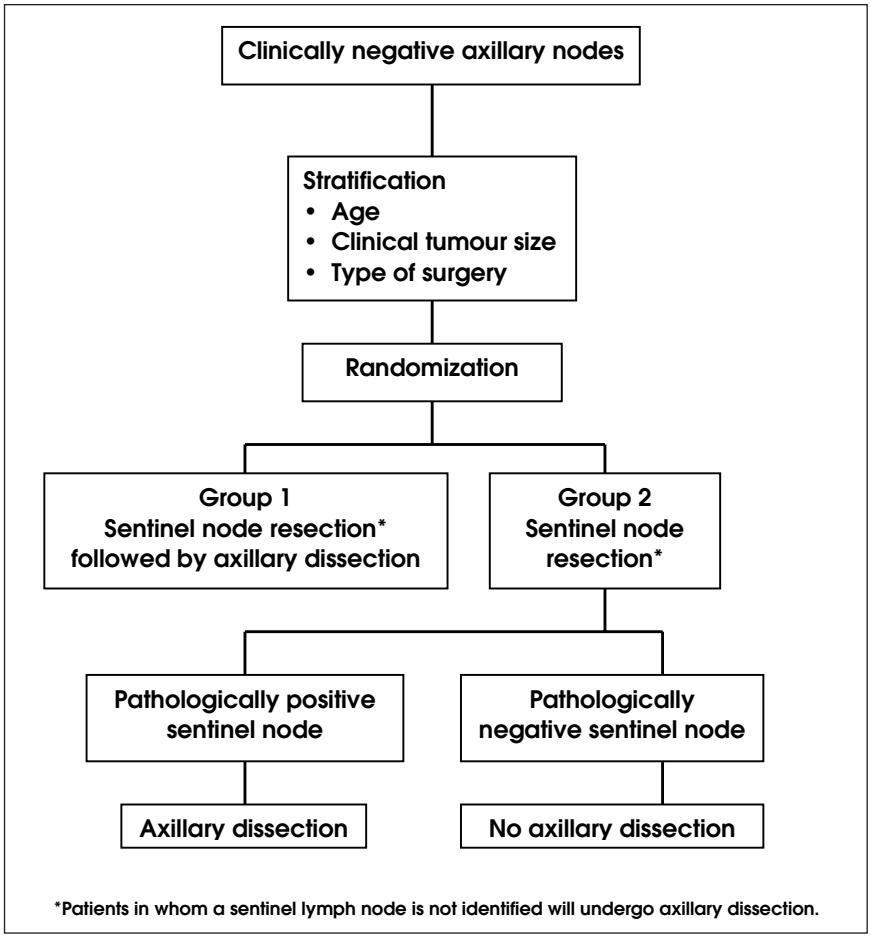

FIG. 1. Algorithm for the management of women with breast cancer and clinically negative axillary nodes in the National Surgical Adjuvant Breast Project trial B32.

particularly those with possible micrometastatic disease, and may well redefine the role of adjuvant therapy. The status of the regional nodal basins still remains the single most important variable predicting prognosis. ALND provides the benefit of regional control of axillary disease and may improve overall survival.[16] Surgical removal of microscopic nodal metastases may be curative in certain populations. It is possible that some patients may be spared the use of adjuvant chemotherapy or offered its use, depending whether micrometastasis can be found with the highly sensitive techniques described.

In addition to clinicopathological parameters such as estrogen-receptor and progesterone-receptor status, tumour size, DNA ploity, degree of angiogenic activity, which the authors and others have studied in detail, molecular markers such as those delineating expression of apoptosis-regulating genes such as *P53* and *BCL-2* or *HER2*-overexpressing tumours may allow prediction of prognosis and chemoresponsiveness.[17] Gene expression arrays technology can identify individual profiles that may predict prognosis or treatment response and, if validated, this approach may enable the selection of patients who could benefit and chemotherapy that will optimize treatment, minimize toxicity and select the right patient for the most effective treatment.

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Correction

In the article "Users' guide to the surgical literature: how to perform a literature search" by Birch and associates in the April issue (*Can J Surg* 2003;46:136-41), figures 2 and 3 were transposed; the legends are correct. We apologize to the authors and our readers for this error.