Is There a Need for Axillary Dissection in Breast Cancer?

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Abstract
The involvement of axillary nodes remains a significant prognostic factor in breast cancer. However, management has changed from complete surgical staging to sentinel lymph node biopsies. Although little controversy exists regarding patients with negative sentinel lymph node biopsies, some remains regarding what to do with patients with small volume of axillary disease. This article focuses on the examination of recent evidence in management of the axilla. It focuses on both the prognostic and therapeutic information gleaned from isolated tumor cells and micrometastatic disease and on the use of completion axillary lymph node dissections or axillary radiation in preventing regional recurrence. (JNCCN 2011;9:225–230)

Although the involvement of axillary nodes remains a significant prognostic factor used in the management of breast cancer, the management of the axilla has changed dramatically. Among women with clinically negative nodes, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial showed no difference in survival among those treated with radical mastectomy (including axillary clearance), simple mastectomy plus radiation without axillary surgery, or simple mastectomy alone.1 This trial, combined with the results of the NSABP B-06 trials, changed the standard therapy from radical mastectomy to breast-conserving therapy, with axillary lymph node dissection (AND) performed for staging and local control.2 In 1994, sentinel lymph node biopsy (SLNB) was adapted to breast cancer and later incorporated into practice standards.3,4 SLNB provides accurate staging and, when negative, does not increase the rate of axillary recurrence when used in place of AND.5 Widespread use of SLNB has markedly reduced the frequency and severity of complications associated with axillary surgery among women with negative nodes.6

A key controversy in the use of SLNB is the role for completion AND (CAD) when the SLNB is positive. The use of SLNB led to more detailed pathologic examination of the sentinel node to identify limited or micrometastatic nodal involvement that previously went undetected. Given the absence of a survival advantage associated with AND, many oncologists question its value, especially in the setting of minimal nodal disease. A recent study that queried members of ASCO found that only 22% would always recommend AND for micrometastatic disease, and that 76% of radiation oncologists would consider axillary radiation instead of axillary dissection for micrometastatic disease.7 This is corroborated by data from the SEER database showing that, between 1998 and 2004, the number of women with positive nodes who did not undergo CAD increased from 20% to 32%.8 Similarly the National Cancer Data Base (NCDB) reported that 20% of patients with positive sentinel nodes treated from 1998 to 2005 did not have AND, and showed a trend to less use of AND over time.9

This article reviews the role of axillary staging, focusing on the prognostic significance of micrometastatic disease, need for enhanced pathologic examination of axillary nodes, need for CAD for women with positive sentinel nodes, and role of radiation in place of axillary dissection.
Prognosis

Lymph node involvement is one of the most discriminating factors affecting breast cancer prognosis and, along with planning of systemic therapy, is the primary justification for axillary surgery. Prognosis is also a function of the number of involved lymph nodes with worsening outcome with higher numbers of positive nodes.\(^\text{10}\) Nonsurgical techniques, including anatomic and functional imaging to define node involvement, have been studied extensively but none have had sufficient accuracy to replace surgical node removal.\(^\text{11,12}\)

With the development of SLNB, fewer nodes required evaluation, and pathology protocols for evaluation of sentinel nodes progressed to multilevel sectioning at 2- to 3-mm intervals, and to the use of immunohistochemistry for cytokeratins.\(^\text{13}\) This identified limited nodal disease that previously may have gone unrecognized and classified as node negative. The 7th edition of the American Joint Committee on Cancer’s (AJCC) Staging Manual classifies clusters of cells smaller than 0.2 mm as isolated tumor cells (ITC), and metastases of 0.2 to 2 mm as micrometastases.\(^\text{13}\) The purpose of the ITC classification is to define very small groups (< 200) of cells. The staging system denotes nodes that are positive for ITC as pN0(i+) and nodes with micrometastases as pN1mi.

ITCs and micrometastases have a separate staging classification because it is unclear whether these have the same prognostic significance as “macrometastases.” Therefore, the use of these findings to define further axillary surgery or systemic therapy is controversial. One of the first studies discussing micrometastatic breast cancer in the axilla was reported in 1971.\(^\text{14}\) This study showed that patients with level I lymph node involvement and only micrometastatic disease had the same survival as those with truly negative lymph nodes. However, review of the NSABP B-04 data showed the opposite: that those with micrometastatic disease had an increased rate of recurrence compared with those with negative nodes.\(^\text{15}\)

Since then, numerous studies have both supported and refuted the prognostic significance of micrometastatic disease. Most recently, 2 studies published in 2009 reached opposite conclusions. The first was a retrospective study involving 790 patients at one American center\(^\text{16}\) that showed no difference in outcome among patients with micrometastatic disease, ITCs, and node-negative disease. As expected, a decrease in survival was seen among those with macrometastatic disease. The second study was a Dutch study, the Micrometastases and Isolated Tumor Cells: Relevant and Robust or Rubbish (MIRROR) study,\(^\text{17}\) that evaluated patients who had ITCs and micrometastases identified retrospectively in the Netherlands Cancer Registry. With a median follow-up of 5.1 years, patients with ITCs or micrometastases had a decreased disease-free survival. A possible explanation for the different conclusions is that the Dutch study primarily included women who, according to the then-accepted treatment standards, underwent no adjuvant systemic therapy, whereas a much higher proportion of the American patients underwent systemic therapy (endocrine and/or chemotherapy).

Against this backdrop of many retrospective reports, 2 prospective studies may answer this question, the NSABP B-32 trial and the American College of Surgeons Oncology Group (ACOSOG) Z-0010 trial. In both studies, women with a negative sentinel node had immunohistochemistry performed at a central study laboratory, and the patients and physicians were blinded to the results. NSABP B-32 randomized women to SLNB alone versus SLNB plus AND to determine if AND improves outcome. Another goal of this study was to determine the significance of immunohistochemistry-detected metastases.\(^\text{18}\) The study showed no role for AND with a negative SLNB, but the immunohistochemistry data have not been reported.\(^\text{19}\) In the Z-0010 trial,\(^\text{20}\) 5184 women underwent SLNB alone and, if negative, were followed up prospectively without AND. In addition, they had bone marrow aspirates sent for central laboratory evaluation for occult metastases. Immunohistochemistry detected 350 additional patients with lymph node disease. Bone marrow occult metastases were seen in 3%. The presence of bone marrow metastases had a significant impact on 5-year survival (90% vs. 95%). However, the presence of immunohistochemistry-detected lymph node metastases had no impact on axillary recurrence, distant recurrence, or survival. Full evaluation of these findings will be forthcoming when the data are peer-reviewed.

Overall, the preponderance of information suggests that ITCs and micrometastases have no impact on prognosis among women who undergo stage-appropriate systemic therapy based on negative nodes, supporting practice guidelines that recommend against routine use of immunohistochemistry with SLNB.\(^\text{21}\)
**Predicting the Presence of Metastases in Nonsentinel Lymph Nodes**

Many have hypothesized that if the risk of additional positive nodes is sufficiently low, AND provides no value. This has led several investigator teams, led initially by van Zee et al.,22 to develop nomograms to predict the likelihood that the remaining nonsentinel lymph nodes are positive. These estimates are based on numerous clinical factors, including the detection method of sentinel lymph nodes (routine hemolysin and eosin staining [H&E], serial sectioning with H&E alone, or cytokeratin immunohistochemistry).

This nomogram has been validated using different patient populations and is better than clinicians at predicting the likelihood of positive non–sentinel lymph nodes.23,24 One of the major criticisms of the van Zee model is that the nomogram does not use the size of the sentinel node metastases and only uses detection by immunohistochemistry as a surrogate for metastasis size.25 Other nomograms have been developed using size as a factor.25 Although these nomograms are reasonably accurate, they do not provide guidance as to when it is appropriate to omit axillary dissection. Whether a 5%, 10%, or 15% risk of additional nodal disease is sufficiently low to justify omitting AND is entirely subjective.

**Treatment Decisions**

The second purported benefit associated with axillary dissection for a woman with positive nodes is that the added information affects systemic and radiation therapy decisions. Historically, systemic therapy recommendations were based partly on the extent or number of positive nodes. However, current guidelines do not stratify systemic therapy recommendations on this basis. Therefore, the role of AND simply to affect systemic treatment decisions is limited. In a retrospective review of patients with immunohistochemistry positive–only sentinel lymph nodes, Pugliese et al.26 found that patients who had a CAD were more likely to undergo chemotherapy, but that it did not influence treatment decisions.

With regard to radiation therapy, the number of involved nodes influences the selection of target volumes and radiation fields. In some cases the number of positive nodes will determine whether postmastectomy radiation is given at all. Therefore, omission of AND when the SLNB is positive may result in overtreatment of women with limited involvement or undertreatment if there are unrecognized additional involved nodes. Notably, the ACOSOG Z-0011 trial examining AND with positive sentinel nodes did not use radiation beyond breast tangential fields and very few nodal recurrences occurred.

Although these findings could suggest that axillary radiation may not be necessary in patients with limited nodal disease identified through SLNB who do not have further AND, the patients on this study received, or at least were offered, stage- and hormone receptor–appropriate adjuvant systemic therapy. A subgroup analysis of patients in the MIRROR study who did not undergo systemic therapy showed that patients with micrometastases who did not have CAD or axillary radiation had a 6% rate of axillary recurrence, whereas those who had AND or axillary radiation only had a 1.2% rate of axillary recurrence at 5 years.27 This underscores the need for multidisciplinary consultation in these cases, and supports the role of axillary treatment in reducing recurrences in patients not undergoing systemic therapy.

A European trial is examining whether axillary radiation is equivalent to CAD in treating patients with early-stage breast cancer with positive SLNB results (the After Mapping of the Axilla: Radiotherapy or Surgery? [AMAROS] trial). An interim analysis in 2010 showed no differences in the use of chemotherapy and endocrine therapy between the groups.28 Multivariate analysis showed that the use of chemotherapy was only affected by primary tumor characteristics and the size of lymph node metastasis. Until the results of the AMAROS trial are reported, patients with minimal nodal disease found on SLNB without CAD are more likely to be offered radiation treatment to the axilla than those for whom CAD confirms only minimal disease in the axilla, especially in those not undergoing adjuvant systemic therapy.

**Local Control**

The final benefit of performing axillary surgery is locoregional control of the axilla. The use of surgery for locoregional control dates back to the original Halsted mastectomy, which included routinely clearing the axilla of lymph nodes.29 After the publication of the NSABP B-04 trial, the idea that breast cancer spreads from the breast systematically to the regional lymph nodes and subsequently metastasizes...
began to be replaced by the idea that positive lymph nodes represent a more aggressive biology. In this trial, 40% of patients with clinically negative lymph nodes had positive lymph nodes when radical mastectomy was performed. Among those randomized to no axillary surgery or radiation, the local failure rate was approximately 20%, but survival was unaffected. More recent studies have shown limited or no impact of axillary surgery on outcome in women with positive nodes. The retrospective study of the NCDB compared women with positive SLNB who had CAD with those who did not. No difference in survival or axillary recurrence was seen among patients who had macrometastatic or micrometastatic disease and elected to not have a CAD.

Ultimately, these questions require controlled clinical trial data. The ACOSOG Z-0011 trial examined the value of CAD among women undergoing breast-conserving surgery who had 1 or 2 positive sentinel nodes. This study randomized women with early-stage breast cancer (T1 or T2 with clinically negative axilla with positive sentinel lymph nodes) to either CAD or no further axillary intervention. In this study, all women underwent breast conservation and whole-breast radiation (no added axillary radiation). Systemic therapy was administered based on physician recommendation. The original accrual goal was 1900, but the study was closed because of accrual difficulty, with only 856 patients available for analysis.

This study found that in patients with positive sentinel lymph nodes who went on to have a CAD, 27% had additional positive axillary nodes and 10% who had micrometastatic disease on SLNB had positive nodes on CAD. However, the group with positive sentinel lymph nodes treated without CAD had the same very low rate of axillary recurrence (0.9% for patients with sentinel lymph nodes only, and 0.5% in patients with CAD) and the same overall survival as those treated with AND. The data were only recently published and are already changing practice for women with nodal disease.

Radiation Therapy

Another question is whether radiation therapy can be given in place of CAD. Radiation therapy provides excellent locoregional control and improves overall survival after mastectomy for women with positive nodes. Radiation may provide local control equivalent to CAD without the complications associated with axillary surgery. Several small retrospective studies have shown a low regional recurrence rate using radiation therapy in place of AND. One randomized trial performed in the 1980s showed significantly more recurrences in the axillary radiotherapy group at 15 years (3% vs. 1%). Despite the report of the ACOSOG Z-0011 trial, clinicians may favor axillary radiation for these patients, although the study itself did not include nodal radiation. The AMAROS trial examining this question is expected to complete accrual this year, but the data will take several years mature. The optimal integration of radiation and surgery in the management of the axilla is still not clear and will evolve over time.

Axillary Complications

One reason clinicians are moving toward less aggressive surgery in the axilla is that axillary surgery can lead to arm morbidity, including restricted range of motion, paresthesias, and lymphedema. Several studies have shown that SLNB results in lower morbidity than AND. Several studies have shown that SLNB results in lower morbidity than AND. Bafford et al. showed an 11% complication rate after AND compared with only a 2.6% complication rate after SLNB. Additionally, one of the planned goals of the NSABP B-32 trial was to assess patient outcomes after SLNB and AND. Patients undergoing SLNB experienced fewer arm symptoms than those undergoing AND, but symptoms with AND improved over time.

The most feared complication is lymphedema. The reported incidence ranges as high as 20% to 30% with AND, especially when combined with extended nodal radiation. In a recently published study assessing risk factors for lymphedema in a population-based sample, Norman et al. found that AND and use of chemotherapy were independent significant risk factors for lymphedema, whereas neither SLNB nor radiation increased the risk of lymphedema. However, SLNB alone may lead to lymphedema, with rates of 5% to 6% reported in single-institution and randomized multicenter trials.

Conclusions

Axillary surgery in the treatment of breast cancer continues to be the standard of care for providing
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prognostic information, guiding therapy, and providing locoregional control. However, increasing data show that some women with limited lymph node involvement do not benefit from completion axillary dissection and may be spared its morbidity. These findings will have a dramatic impact on breast cancer care. Coupled with increased understanding of cancer biology and its impact on prognosis and therapy, these data are moving the field toward a time when therapy can be truly personalized, and perhaps axillary surgery can even be omitted altogether.

References


