How I Treat Breast Cancer With Positive Lymph Nodes

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Overview

- A metastatic workup is useful for patients with clinical stage III disease.
- Consider neoadjuvant chemotherapy for patients with lymph node–positive disease.
- Most patients can be treated with sentinel lymph node biopsy, except those presenting with inflammatory breast cancer.
- The need for completion axillary dissection depends on the number of nodes involved, the size of the node deposit(s), plans for postoperative radiation therapy, and other factors.
- Targeted axillary dissection, in which the surgeon not only performs a sentinel node biopsy but also removes a previously clipped positive node that is identified by a radioactive seed, has become popular in some centers.
- Radiation therapy, whether after breast-conserving surgery or mastectomy, should be considered for patients with node-positive disease.

Introduction

Of the 268,000 patients in whom breast cancer is diagnosed in the United States each year,[1] approximately 32% have positive lymph nodes at the time of diagnosis.[2] Suspicious lymph nodes are often detected on clinical breast examination, mammography, or ultrasonography. The diagnosis of positive lymph nodes, however, requires fine-needle aspiration or a core needle biopsy. A simplified schema of my approach to patients with breast cancer who present with biopsy-proven positive nodes is shown in the Figure.

Metastatic Workup

Node positivity remains an important prognostic indicator and is a key aspect of breast cancer staging. Although the majority of patients who present with clinically node-positive disease do not have concomitant distant metastasis, current guidelines suggest that patients who present with clinical stage III (T3N1) disease or symptoms concerning for metastatic spread should undergo a staging workup.[3] Should there be evidence of metastatic disease, locoregional management of the breast and axilla becomes palliative, and systemic therapy is considered as appropriate. However, if patients present with T0-2N1 disease and/or are found not to harbor distant metastases at the time of presentation, treatment proceeds with curative intent, as discussed below.

Neoadjuvant Chemotherapy

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial demonstrated conclusively that the strategies of adjuvant and neoadjuvant chemotherapy are equally efficacious in terms of survival.[4] Hence, for patients with node positivity who will require chemotherapy as part of their treatment regimen, a neoadjuvant approach should be considered. This approach not only allows tumor shrinkage, which makes breast-conserving surgery more feasible for some patients, but also provides an in vivo mechanism for evaluating response to treatment. A pathologic complete response may be achieved in up to 80% of patients (depending on tumor subtype and definition of pathologic complete response) treated in the neoadjuvant setting[5]; this not only portends a better prognosis but also may result in a downstaging of disease and minimize the need for axillary dissection with its attendant complications.

Although there was some concern initially regarding the validity of sentinel node biopsy after neoadjuvant therapy, a number of studies have now shown a high rate of sentinel node identification and a low false-negative rate with this technique.[6] The main advantage of undertaking a sentinel node biopsy after neoadjuvant chemotherapy (rather than before it is initiated) is the potential to downstage initially node-positive disease, rendering

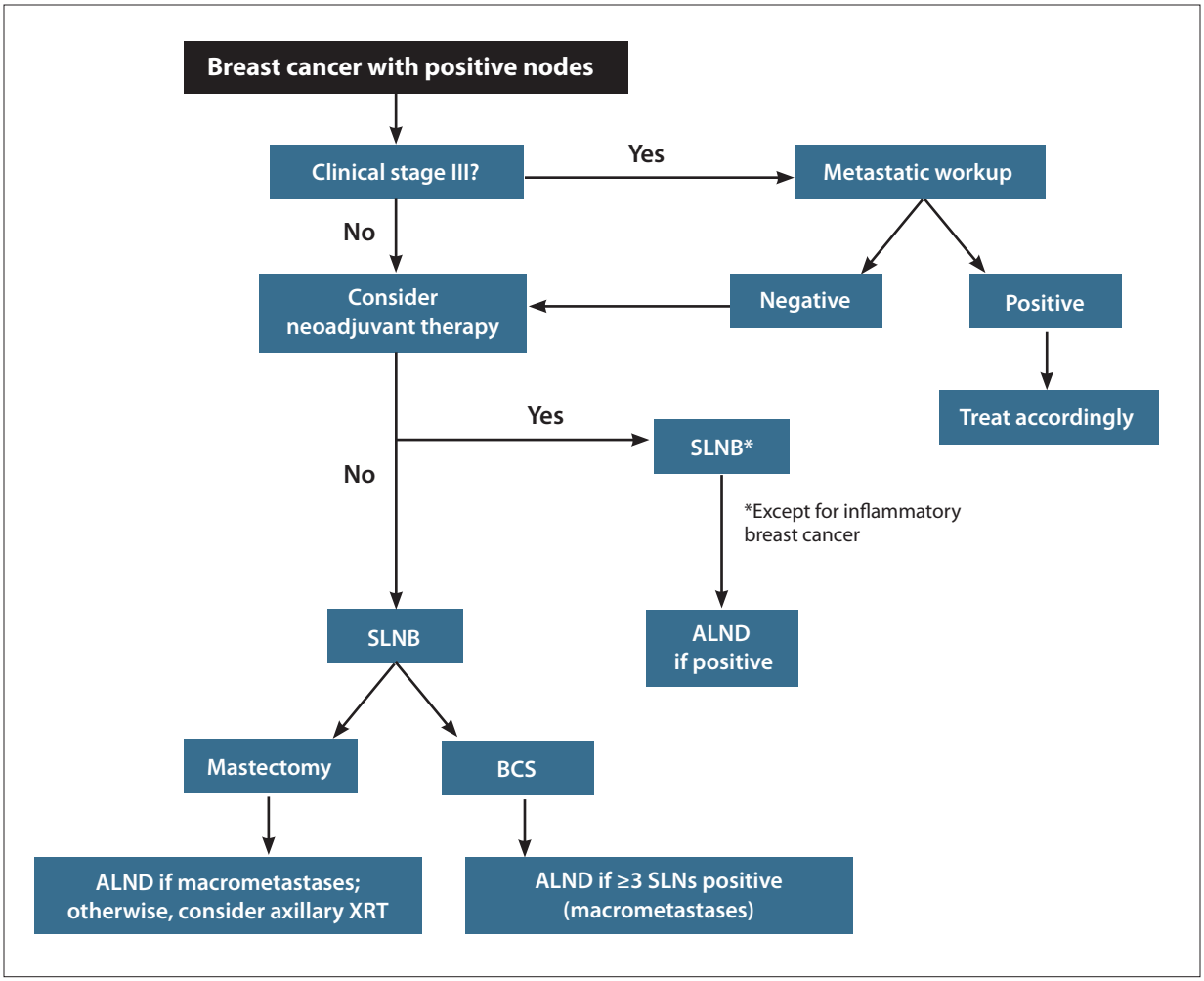

Figure. Treatment algorithm for patients who have breast cancer with positive nodes.

ALND, axillary lymph node dissection; BCS, breast-conserving surgery; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; XRT, external radiation therapy.

it node-negative. Downstaging obviates the need for a completion axillary node dissection in most cases.

The exception to this approach is inflammatory breast cancer, in which the feasibility and accuracy of sentinel node biopsy remain questionable. A small feasibility trial of sentinel node biopsy after neoadjuvant chemotherapy in the setting of inflammatory breast cancer found that sentinel node mapping failed in 75% of patients.[7]

Outside this context, however, sentinel node biopsy after neoadjuvant chemotherapy seems to be fairly successful. Several meta-analyses have found rates of sentinel node identification to be 63% to 100% following neoadjuvant chemotherapy, with false-negative rates of 0% to 39%.[6] The American College of Surgeons Oncology Group (ACOSOG) Z1071 trial found that the rate of sentinel node identification after neoadjuvant chemotherapy was 92.5%, the accuracy was 91.7%, and the overall false-negative rate was 14.7%.[8] The SENTINA (Sentinel Neoadjuvant) trial reported a similar false-negative rate of 14.2%, although the rate of sentinel node identification after neoadjuvant chemotherapy in that trial was much lower, at 80.2%.[9] The SN FNAC (Sentinel Node Biopsy Following Neoadjuvant Chemotherapy) trial reported a sentinel node identification rate of 87.6%; the false-negative rate depended on how a positive node was defined.[10] When the presence of isolated tumor cells was considered to be positivity, the false-negative rate was 8.4%; however, when only micrometastases and larger metastases were considered to be positivity (as in the other 2 trials), the SN FNAC trial found a false-negative rate of 13.3%.[10]

All of these trials used similar means of reducing the false-negative rate associated with sentinel node biopsy after neoadjuvant chemotherapy. For example, removing

at least 2 sentinel nodes resulted in a false-negative rate of 12.8% in the ACOSOG Z1071 trial. The SENTINA trial reported that taking more than 1 sentinel node significantly lowered the odds of a false-negative result (odds ratio, 0.505; 95% CI, 0.306-0.833; *P*=.008), and the SN FNAC trial found that taking more than 1 sentinel node reduced the false-negative rate from 18.2% to 4.9%.[10]

Similarly, the use of dual-tracer imaging has been found to be helpful in reducing the false-negative rate associated with sentinel node biopsy after neoadjuvant chemotherapy. In the ACOSOG Z1071 trial, the false-negative rate dropped to 10.8% when dual-tracer imaging was used.[8] Similarly, in the SN FNAC trial, the false-negative rate of sentinel node biopsy when radioisotope was used alone was 16.0%, but this dropped to 5.2% when the procedure was performed with both isotope and blue dye.[10]

Some authors have suggested that placing a titanium clip at the time of initial core biopsy of suspicious lymph nodes may reduce the false-negative rate of sentinel node biopsy after neoadjuvant chemotherapy for patients with node positivity, as one can ensure that the clipped node has been removed at the time of the sentinel node biopsy. In the ACOSOG Z1071 trial, a clip was placed in 203 patients at the time of the initial core biopsy and 2 or more sentinel nodes were identified in 170 of these patients. The clip was identified in one of the sentinel nodes in 62.9% of these patients and during axillary dissection in 20.0% of them; the clip was not identified 17.1% of cases.[11] The false-negative rates associated with these 3 scenarios were 6.8%, 19.0%, and 14.3%, respectively.[11] The false-negative rate associated with sentinel node biopsy after neoadjuvant chemotherapy in the 355 patients in the ACOSOG Z1071 trial, in whom no clip was placed, was 13.4%.[11] Although these data suggest that placement of a clip may be helpful in lowering the false-negative rate associated with sentinel node biopsy after neoadjuvant chemotherapy, this is true only if one can verify that the clipped node has been removed in the sentinel node biopsy. Often, a clipped node is not localized with a preoperatively placed wire, and therefore (at least at centers using needle/wire localization for nonpalpable lesions) it may be difficult to find the clipped node if the clip is not confirmed to have been removed with one of the sentinel nodes, found in the usual fashion by using radioactive tracer and blue dye. Some are now advocating that other localization devices, such as radioactive seeds[12] or other devices,[13] be placed in the nodes so that these nodes may be more easily identified.

Caudle and colleagues at MD Anderson Cancer Center pioneered the concept of targeted axillary dissection, in which a standard sentinel node biopsy is combined with the removal of any clipped node, identified by a preoperatively placed radioactive seed. In their study of 191 patients who underwent this procedure followed by axillary node dissection, the false-negative rate after sentinel node biopsy alone was 10.1%. After evaluation of the clipped node, however, the false-negative rate dropped to 1.4%. The clipped node was not a sentinel node in 23% of the patients, including 6 patients in whom the sentinel node was negative but metastases were identified in the clipped node.[12]

> Clinical trial data indicate that less aggressive surgery is possible without compromising good oncologic outcomes.

The fervor with which we pursue the lowest possible false-negative rate, however, may wane with time and additional data. It is clear that many of the patients with node positivity will require radiation therapy (even after mastectomy), and that this therapy will generally cover the lower two-thirds of the axilla. The effect of radiation therapy as opposed to completion axillary dissection after the identification of a positive sentinel node in the setting of neoadjuvant chemotherapy is currently being studied in the Alliance A11202 trial and the NSABP B-51 trial. We expect to see residual disease in the axilla of 60% to 70% of these patients. If radiation therapy is found to be equivalent to surgery in this setting, chasing the lowest possible false-negative rate for sentinel node biopsy after neoadjuvant therapy will become less important.

Primary Surgery

Certainly, our approach to managing the axilla in patients who have node-positive disease treated with primary surgery has significantly changed over the years. The 2002 NSABP B-04 trial clearly established that removing axillary nodes did not affect survival[14]; hence, the main objectives of axillary management were to stage the disease and provide local control. With the advent of sentinel node biopsy in the mid-1990s, a minimally invasive technique was established for staging the axilla (especially in patients with node-negative disease).[15] The concept that we need to dissect the axilla only in those patients with node

positivity spared the majority of patients the morbidity of more aggressive surgery.[16,17] Nomograms and prediction rules sought to predict the likelihood of non–sentinel node metastases, but at the end of the day, perhaps the greatest effect on our surgical management of the axilla was a result of the ACOSOG Z0011 trial.[18]

The ACOSOG Z0011 trial confirmed the findings of NSABP B-06, in that it found no survival difference between those patients with node positivity who underwent sentinel node biopsy alone followed by radiation therapy and those who underwent a completion axillary dissection. Of note, however, was that the axillary lymph node recurrence rate was low in both arms. At 10 years, the cumulative incidence of lymph node recurrence was 0.5% in the axillary node dissection arm and 1.5% in the sentinel node biopsy arm, despite the fact that 27.3% of the individuals in the axillary dissection arm had further disease in non-sentinel nodes.[18] Given these data, our management of the axilla in patients with node positivity has changed dramatically, such that in patients with node positivity meeting the inclusion criteria for the ACOSOG Z0011 trial, we do not routinely dissect the axilla. It is important, however, to keep in mind the inclusion criteria for the ACOSOG Z0011 trial. This trial included only patients who underwent primary partial mastectomy with whole-breast radiation therapy for invasive breast cancers smaller than 5 cm, with 1 to 2 positive nodes.

The International Breast Cancer Study Group (IBCSG) 23-01 trial had slightly different inclusion criteria, but essentially similar results. This trial randomly assigned patients with invasive breast cancers smaller than 5 cm who had 1 or more micrometastases (<2 mm) and underwent primary surgery (whether mastectomy or breast-conserving surgery) to completion axillary node dissection or not. Of note, 9% of patients in this trial underwent a mastectomy, and 3% of those who had breast-conserving surgery did not have radiation therapy. At a median follow-up of 5 years, the rates of regional recurrence in both the axillary dissection arm and the no axillary dissection arm were approximately 1%, and survival rates were equivalent in the 2 groups.[19] Thus, for patients undergoing mastectomy or undergoing breast-conserving surgery with no plan for whole-breast radiation therapy, an axillary dissection may still be avoided on the basis of these data as long as the positive nodes contain only micrometastases.

Finally, the AMAROS (After Mapping of the Axilla: Radiotherapy Or Surgery) trial, also known as European Organisation for Research and Treatment of Cancer (EORTC) 10981-22023, randomly assigned patients with node positivity to either axillary dissection or axillary radiotherapy. Although the inclusion criteria for this trial included both mastectomy and breast-conserving surgery, approximately 10% of the "node-positive" patients had isolated tumor cells alone, which would now be considered node negativity. Regardless, with a median follow-up of 6.1 years, the authors found no difference in overall survival and disease-free survival between the 2 groups and a low (<1%) risk for axillary recurrence, regardless of the randomization group.[20] These data suggest that the pool of patients in whom an axillary dissection can be avoided could be further widened, limiting the morbidity associated with the surgical approach.

Radiation Therapy

Radiation therapy provides a useful adjunct to surgery by ensuring optimal local control in patients with node positivity. For patients undergoing breast-conserving surgery, radiation therapy has been shown to reduce locoregional recurrence and is therefore part of the current standard of care. When radiation therapy is delivered in tangential fields, it often covers the lower two-thirds of the axilla; hence, in both the ACOSOG Z0011 and AMAROS trials, radiation therapy was mandated as an alternative to axillary dissection.

For patients undergoing mastectomy, the value of postmastectomy radiation therapy, particularly for patients with 1 to 3 positive nodes, is more controversial. Certainly, the most recent guidelines acknowledge the survival benefit of postmastectomy radiation therapy in this subset of patients, but they note that the risk for locoregional failure may be quite low in some patients; hence, they advocate that treatment decisions be tailored to individual patients.[21] Patients with at least 1 macrometastasis (>2 mm) who undergo mastectomy, however, do not fit the inclusion criteria for the IBCSG 23-01 trial, and therefore an axillary dissection may be required for them should postmastectomy radiation therapy be omitted.

Conclusion

The management of patients with node-positive breast cancer requires a multidisciplinary approach, and considerations for neoadjuvant chemotherapy and adjuvant radiation therapy affect surgical decision making in terms of management of the axilla. During the last several years, a dramatic transformation has occurred in terms of how these patients are managed, particularly from a surgical standpoint; clinical trial data indicate that less aggressive surgery (and therefore a corresponding reduction in postoperative morbidity) is possible without compromising good oncologic outcomes. As we push the envelope even further in terms of optimizing the management of these patients, their participation in robust clinical trials will continue to be important.

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