

# ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Guest Section Editor: Ruth O'Regan, MD

## Breast Cancer in Focus

### Management of the Axilla in Breast Cancer Patients Undergoing Neoadjuvant Therapy



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**H&O** Can you briefly review how management of the axilla in breast cancer has changed in recent years?

**JW** Management of the axilla has changed dramatically over the past 2 decades. When I started my training in the early 1990s, every patient with breast cancer had axillary lymph node dissection (ALND), during which an average of 15 to 17 lymph nodes were removed. This commonly caused morbidity, such as longer healing times after surgery, numbness, reduced arm motion, and lymphedema. By the mid- to late-1990s, sentinel lymph node (SLN) biopsy—in which 1 to 3 lymph nodes were typically removed—emerged into breast cancer practice. With SLN biopsy, the risk of lymphedema and other morbidities was reduced. This led to the omission of ALND in those who had negative—and now even some positive—sentinel lymph nodes.

As far as radiation is concerned, numerous analyses from clinical trials have been reported over the last several years that are influencing axillary management. Three of these in particular are notable. The first is the meta-analysis of numerous clinical trials by the Early Breast Cancer Trials Collaborative Group that was published in the *Lancet* in 2005. This study demonstrated that regional radiation improved both survival and locoregional control of breast cancer in women who had undergone a mastectomy and had positive axillary lymph nodes.

The MA.20 clinical trial from the National Cancer Institute of Canada Clinical Trials Group, which was presented at the 2011 American Society of Clinical Oncology (ASCO) meeting, also found benefit from regional nodal radiation. In this study, radiation to the regional lymph nodes improved disease-free survival in women with positive lymph nodes who had undergone breast-conserving surgery.

More recently, at the 2013 ASCO meeting, results were reported from the European Organisation for Research and Treatment of Cancer (EORTC) AMOROS (After Mapping of the Axilla: Radiotherapy or Surgery?) clinical trial, in which women with a positive SLN biopsy were randomized to either ALND or radiation of the lymph nodes. Radiation of the lymph nodes provided cancer control in the axilla that was just as good as ALND, with much less lymphedema.

To summarize, the trend that emerges for management of the axilla is less extensive surgery and more frequent use of regional nodal radiation.

**H&O** In what ways does the use of neoadjuvant chemotherapy affect management of the axilla?

**JW** The answer is evolving with further investigation, which is underway. There are no prospective randomized clinical data addressing when regional nodal radiotherapy should be optimally used following neoadjuvant

chemotherapy. The studies I mentioned all involved axillary lymph node–positive patients who had surgery up front and then underwent adjuvant chemotherapy. If as a result of neoadjuvant chemotherapy the axillary lymph nodes are downstaged pathologically from positive to negative, it is unknown which factors should be used to decide when to deliver radiation. We do not know if the initial positive lymph nodes prior to chemotherapy or the negative lymph nodes after neoadjuvant chemotherapy should be the determining factor in whether regional radiotherapy is indicated.

We do know that neoadjuvant chemotherapy is prognostic for patients who have a complete pathologic response in the breast and/or the lymph nodes. Women whose tumors have a good response to chemotherapy have better disease-free survival than those whose tumors do not have a response to chemotherapy. Therefore, it seems logical that a patient's chemotherapy response should be useful in predicting the benefit from regional radiotherapy. This approach is the subject of an accruing phase 3 clinical trial.

### **H&O** Does neoadjuvant chemotherapy affect the accuracy of SLN biopsy?

**JW** That depends on the number of sentinel lymph nodes removed and the method of detection at the time of SLN biopsy. Two recently reported clinical trials have studied this. The first was the SENTINA (Sentinel Neoadjuvant) trial from Germany and Austria, which was published in *Lancet Oncology* in 2013. The second was the ACOSOG Z1071 trial from the American College of Surgeons Oncology Group, which was published in the *Journal of the American Medical Association* in October 2013. These trials found that the accuracy of the SLN biopsy after neoadjuvant chemotherapy was improved when more than 2 sentinel lymph nodes were recovered and when both radiocolloid and blue dye were used for detection.

### **H&O** Are there any special steps related to the axilla that should be taken before initiating neoadjuvant therapy?

**JW** The special step that is recommended is a more thorough determination of the pathologic status of the axillary lymph nodes prior to neoadjuvant chemotherapy. I recommend that in addition to a good clinical evaluation, breast cancer patients should have an ultrasound or other imaging study and suspicious lymph nodes should be biopsied using fine needle aspiration or core needle biopsy.

I generally do not favor SLN biopsy prior to neoadjuvant chemotherapy because the lymph nodes that are removed are the only positive nodes in approximately half

of cases. Removing these cancerous lymph nodes would destroy the ability to determine important prognostic information for the patient based on neoadjuvant chemotherapy response.

### **H&O** Do you recommend restaging the axilla after the use of neoadjuvant chemotherapy?

**JW** Assessment of neoadjuvant chemotherapy response in the breast and axilla with repeat imaging is indicated prior to surgery. Typically, additional specific restaging of the axilla is not recommended unless the patient has responded poorly to chemotherapy or there is a concern about progression.

### **H&O** Do you recommend radiation after mastectomy based on staging that is done before or after chemotherapy?

**JW** It is unclear whether the indication for radiotherapy after mastectomy should be the clinical stage prior to chemotherapy or the downstaged pathologic stage from surgery afterward. The National Surgical Adjuvant Breast and Bowel Project (NSABP) and Radiation Therapy Oncology Group (RTOG) are enrolling patients in a phase 3 clinical trial—NSABP B-51/RTOG 1304—that will address this question. The study is open to women whose cancer has been confirmed in the axillary lymph nodes prior to neoadjuvant chemotherapy, and afterward are downstaged to having lymph nodes that are pathologically clear of cancer at the time of surgery. Women who have a mastectomy will be randomized to either observation or radiation of the chest wall and regional lymph nodes. Women who have a lumpectomy will be randomized to either breast radiation alone or breast and lymph node radiation.

The goal of this trial is to find out whether women who have positive lymph nodes before neoadjuvant therapy that get downstaged afterward to pathologically clear are benefited by the radiation in terms of lower rates of breast cancer recurrences.

### **H&O** Are any other trials investigating the effect of neoadjuvant therapy on treatment?

**JW** The other important study is Alliance A011202 from the Alliance in Oncology, a National Cancer Institute Cooperative Group. This study is asking the question of whether we can eliminate ALND in patients who have positive lymph nodes before neoadjuvant chemotherapy that continue to be positive afterwards at the time of SLN biopsy. All of the patients enrolled in the study will go on to receive regional nodal radiation and will be randomized to receive either ALND or no ALND.

Between NSABP B-51/RTOG 1304 and this trial, we hope to answer the question of how to appropriately manage the axilla in women who have had neoadjuvant chemotherapy, whether they remain node-positive or become node-negative.

### Suggested Readings

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