

## Position Statement on Management of the Axilla in Patients with Invasive Breast Cancer

Sentinel lymph node (SLN) biopsy has replaced axillary lymph node dissection (ALND) for the staging of clinically node-negative breast cancer patients, demonstrating equivalent survival to ALND for lymph node-negative patients<sup>1</sup> while resulting in reduced morbidity.<sup>2</sup> For the majority of patients with pathologically positive SLNs, completion ALND is recommended by the American Society of Clinical Oncology Guidelines and the National Comprehensive Cancer Network (NCCN).<sup>3,4</sup> However, recent data from the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial suggest that ALND may be omitted in selected patients with 1 or 2 positive SLNs.<sup>5,6</sup>

In the ACOSOG Z0011 trial, 813 patients with clinical T1-2 node-negative tumors who were found to have hematoxylin and eosin (H&E)-positive SLNs were randomized to ALND vs no further axillary surgery. Patients with palpable lymph nodes or clinical T3 tumors were not eligible for this study. The protocol mandated the use of standard whole-breast radiation without an axillary field. Patients with  $\geq 3$  positive SLNs were excluded from the study. The trial was closed early due to poor accrual with an enrollment of only 47% of the targeted 1900 patients. It still showed equivalent results between the 2 treatment arms for loco-regional failure and survival. At 6.3 years' follow-up, no differences were found between the 2 groups in the rates of axillary recurrence (0.5% vs 0.9%), in-breast recurrence (3.6% vs 1.9%), or overall locoregional recurrence (4.1% vs 2.8%,  $P = 0.53$ ).<sup>5</sup> Disease-free and overall survival were similar (82.2% vs 83.8% and 91.9% vs 92.5%) between the groups.<sup>6</sup> The majority of women in this trial were older than 50 years (64%), had clinical T1 tumors (68%), had ER-positive tumors (77%), had only 1 positive SLN (60%), received whole-breast radiation (89%), and received systemic therapy (96%: 58% adjuvant chemotherapy and 46% adjuvant hormonal therapy). Forty percent of patients had micrometastases or isolated tumor cells and 60% had macrometastases in the sentinel nodes. Additional positive axillary nodes were found in 27.3% of the ALND patients. This study excluded patients undergoing mastectomy and patients receiving neoadjuvant chemotherapy.

**The results from ACOSOG Z0011 are potentially practice changing and ALND may no longer be routinely required for patients who meet *all* of the following criteria:**

- T1-2 tumors
- One to two positive SLNs without extracapsular extension
- Patient acceptance and completion of whole-breast radiation therapy without extended fields of therapy
- Patient acceptance and completion of adjuvant therapy (hormonal, cytotoxic, or both)

**The results from ACOSOG Z0011 are *not* directly applicable to patients who**

- Have T3 tumors
- Have more than 2 positive nodes

- Are undergoing mastectomy
- Are undergoing partial breast radiation
- Have been identified as having matted axillary nodes or preoperative palpable nodes
- Are receiving neoadjuvant chemotherapy (*See below.*)

## **Pathology, Immunohistochemistry, and SLN Biopsy**

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**The prognostic significance of SLN disease detected on immunohistochemistry (IHC) has been widely debated and results from 2 recent studies indicate that SLN micrometastases detected by IHC staining are clinically insignificant and routine use of IHC can be abandoned.** In the ACOSOG Z0010<sup>7</sup> and National Surgical Adjuvant Breast and Bowel Protocol (NSABP) B-32<sup>8</sup> trials, all patients were treated on the basis of H&E SLN stains only. To control for treatment bias, clinicians and patients were blinded to the results of IHC staining. In ACOSOG Z0010, a prospective observational study of SLN biopsy, occult metastases were found by IHC in 8.9% of 3945 patients who were SLN-negative by H&E: 5-year survival was not different between those patients who were H&E negative and IHC negative, and those who were H&E negative and IHC positive (95.8% vs 95.1%,  $P = 0.53$ ).<sup>7</sup> In NSABP B-32, a prospective randomized study of SLN biopsy plus ALND vs SLN biopsy alone (with ALND limited to SLN-positive patients), occult metastases were found by IHC in 15.9% of 3887 H&E-negative patients. Although overall, disease-free and distant disease-free survival were significantly worse for IHC-positive than for IHC-negative patients, the absolute difference in overall survival was only 1.2% (94.6% vs 95.8%,  $P = 0.03$ ).<sup>8</sup>

The results of the ACOSOG Z0010 and NSABP B-32 trials suggest that SLN micrometastases found only by IHC are clinically insignificant and that IHC staining of SLNs is unnecessary; therefore, routine use of IHC staining of SLNs is not recommended and should be limited to selective use at the discretion of the pathologist. In addition, intraoperative frozen-section analysis of the SLN can be avoided if clinical suspicion of nodal involvement is low and the patient otherwise meets the entry criteria for the Z-11 trial.

The data are fairly clear for the above recommendations. There are two additional areas where the data are less clear and the management is still evolving:

### **Sentinel Lymph Node Biopsy and Neoadjuvant Systemic Therapy**

An area of controversy exists in the use of SLN biopsy after preoperative systemic therapy due to the possibility of nonuniform, selective “sterilization” of lymph nodes. In this scenario, a negative SLN biopsy may still be associated with lymph nodes that harbor metastatic disease, resulting in reduced accuracy and unacceptably high false-negative rates. Studies thus far, however, do not support this theory and overall demonstrate similar accuracy and false-negative rates, especially in patients with a clinically negative axilla prior to systemic therapy. The largest published study evaluating SLN biopsy after preoperative chemotherapy came from the NSABP B-27 trial, in which 428 patients had SLN biopsy followed by completion axillary dissection.

SLNs were successfully identified in 85% and the false-negative rate was 11%.<sup>9</sup> A meta-analysis of 21 published studies, which included 1273 patients who underwent SLN biopsy with subsequent axillary dissection after preoperative chemotherapy, reported an SLN identification rate of 90% and a false-negative rate of 12%.<sup>10</sup> These results are similar to reported data from the NSABP B-32 trial, which compared SLN resection with conventional ALND for node-negative breast cancer patients.<sup>11</sup>

On the other hand, a small retrospective analysis of SLN biopsy after preoperative chemotherapy reported a higher false-negative rate (25%) in patients who had cytologically documented axillary lymph node involvement prior to chemotherapy.<sup>12</sup> However, in the NSABP B-27 trial, the false-negative rate was not different for clinically node-positive patients. The role of SLN biopsy in patients with clinically positive axillae undergoing induction chemotherapy is being evaluated by the ACOSOG trial Z1071. The study is investigating SLN surgery after neoadjuvant chemotherapy for stage II, stage IIIA, and stage IIIB breast cancer patients who have documented axillary lymph node metastases prior to systemic therapy. This trial also takes advantage of the use of pre-systemic therapy axillary ultrasound (US); in the event of a suspicious axillary US, a fine-needle aspiration (FNA) or core biopsy is performed to document the presence of metastasis. All patients will undergo a SLN biopsy followed by completion ALND to determine the utility of SLN biopsy in this clinical scenario.

Data actually documenting the utility of SLN biopsy in patients with inflammatory breast cancer are limited. An early report of 8 patients showed an inability to identify an SLN in 1 patient and a false-negative SLN in 2 patients, resulting in a false-negative rate of 25%.<sup>13</sup> Another study evaluated the utility of SLN biopsy after induction chemotherapy in 20 patients with inflammatory breast cancer and a clinically negative axilla using only vital blue dye.<sup>14</sup> The authors found a low identification rate of 80%, and 2 patients had false-negative SLNs for an overall false-negative rate of 18%.

In summary, patients who are node-negative, based on clinical examination, radiological examination, and/or FNA, may undergo SLN biopsy after completion of preoperative systemic therapy at the same time as the surgical treatment of their primary breast cancer. It is uncertain whether patients in whom clinical examination is positive prior to initiating preoperative systemic therapy are candidates for SLN biopsy if they undergo axillary downstaging following their systemic therapy. The large ACOSOG Z1071 trial will help define the utility of SLN biopsy after preoperative systemic therapy in this subgroup of patients. Insufficient data exists to support the use of SLN biopsy in patients with inflammatory breast cancer.

## **Radiation Therapy**

The use of axillary radiation as an alternative to ALND has been evaluated in breast cancer patients with clinically negative axilla. Older trials have demonstrated no difference in survival between patients who undergo axillary irradiation vs ALND.<sup>15</sup> Due to the inherent loss of staging information without an ALND, axillary irradiation in lieu of ALND has not been adopted into clinical practice. While axillary radiation may be an alternative to axillary

dissection in women with clinically node-negative breast cancer, there is limited data regarding its utility in patients after a positive SLN biopsy. The currently ongoing European Organisation for Research and Treatment of Cancer (EORTC) After Mapping of the Axilla: Radiotherapy Or Surgery (AMAROS) study randomizes patients with positive SLNs to axillary dissection vs axillary radiation, regardless of type of original surgery (mastectomy or breast conservation therapy) or size and number of positive SLNs. The results of this study may alter treatment recommendations in the future.<sup>16</sup> Further decision-making regarding use of axillary radiation in lieu of ALND needs to be made in the context of a multidisciplinary discussion, involving radiation oncology, medical oncology, and surgery, that takes into account patient and cancer characteristics and treatment goals.

## - References -

1. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary lymph node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomized phase 3 trial. *Lancet Oncol.* 2010;11:927-933.
2. Purushotham AD, Upponi S, Klevesath MB, et al. Morbidity after sentinel lymph node biopsy in primary breast cancer: results from a randomized controlled trial. *J Clin Oncol.* 2005;23:4312-4321.
3. Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. *J Clin Oncol.* 2005;23:7703-7720.
4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology—V.2.2011. Available at: [http://www.nccn.org/professionals/physician\\_gls/PDF/breast.pdf](http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf). Accessed July 12, 2011.
5. Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg.* 2010;252:426-432; 432-433 [discussion].
6. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA.* 2011;305(6):569-575.
7. Hansen NM, Grube B, Ye X, Roderick Turner RR, Brenner RJ, Sim M, Giuliano AE. Impact of micrometastases in the sentinel node of patients with invasive breast cancer. *J Clin Oncol.* 2009;27:4679-4684.
8. Weaver DL, Ashikaga T, Krag DN, et al. Effect of occult metastases on survival in node-negative breast cancer. *N Engl J Med.* February 3, 2011;364(5):412-421.
9. Mamounas EP, Brown A, Anderson S, et al. Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol.* 2005;23(12):2694-2702.
10. Xing Y, Foy M, Cox DD, Kuerer HM, Hunt KK, Cormier JN. Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer. *Br J Surg.* 2006;93(5):539-546.
11. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary- lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol.* 2011;11(10):927-933.
12. Shen J, Gilcrease MZ, Babiera GV, et al. Feasibility and accuracy of sentinel lymph node biopsy after preoperative chemotherapy in breast cancer patients with documented axillary metastases. *Cancer.* 2007;109(7):1255-1263.
13. Stearns V, Ewing CA, Slack R, Penannen MF, Hayes DF, Tsangaris TN. Sentinel lymphadenectomy after neoadjuvant chemotherapy for breast cancer may reliably represent the axilla except for inflammatory breast cancer. *Ann Surg Oncol.* 2002;9(3):235-242.
14. Hidar S, Bibi M, Gharbi O, et al. Sentinel lymph node biopsy after neoadjuvant chemotherapy in inflammatory breast cancer. *Int J Surg.* 2009;7(3):272-275.
15. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med.* 2002;347(8):567-575.
16. Straver ME, Meijnen P, van Tienhoven G, et al. Sentinel node identification rate and nodal involvement in the EORTC 10981-22023 AMAROS trial. *Ann Surg Oncol.* 2010;17(7):1854-1861.

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