Management of the Axilla

A series of classic randomized trials, including NSABP-B-04, formed the basis for level I and II axillary-node dissection becoming a standard of care for women with invasive breast cancer. The emergence of sentinel lymph node biopsy (SLNB) as an initial staging procedure led to a new generation of trials evaluating the need for axillary dissection in women with pathologically negative or positive nodes. Recently reported results from NSABP-B-32 and the ALMANAC trial support the use of SLNB for women with clinically node-negative disease. Preliminary data indicate that SLNB has a nine to 10 percent false-negative rate. SLNB can also significantly reduce postoperative arm morbidity.

PHASE III PROGNOSTIC STUDY OF SENTINEL NODE AND BONE MARROW MICROMETASTASES IN WOMEN WITH STAGE I OR IIA BREAST CANCER

Protocol IDs: ACOSOG-Z0010, GUMC-00152
Accrual: 5,300 (Closed)

Eligibility	Stage I or IIA breast carcinoma within 60 days of planned sentinel lymph node biopsy
Protocol	Bilateral anterior iliac crest bone marrow aspiration to test for micrometastases → lumpectomy + sentinel lymph node biopsy
	Sentinel node + → ACOSOG-Z0011

All patients receive whole breast radiation therapy (excluding a supraclavicular field) five days a week for a maximum of eight weeks and systemic adjuvant therapy as indicated.

Patients with no sentinel node identified intraoperatively and patients with sentinel node metastases identified by H&E who chose not to be registered to ACOSOG-Z0011 undergo axillary lymph node dissection.

SOURCE: NCI Physician Data Query, January 2005.

PHASE III RANDOMIZED STUDY OF SENTINEL NODE DISSECTION WITH OR WITHOUT CONVENTIONAL AXILLARY DISSECTION IN WOMEN WITH CLINICALLY NODE-NEGATIVE BREAST CANCER

Protocol ID: NSABP-B-32
Accrual: 5,611 (Closed)

Eligibility	Clinically node-negative breast cancer
ARM 1	Sentinel lymph node biopsy with axillary dissection
ARM 2	Sentinel lymph node biopsy → positive → axillary dissection → negative → no axillary dissection

If no sentinel node is identified, patients undergo axillary dissection. Patients with cytologically negative but histologically positive sentinel nodes undergo axillary dissection.

PRELIMINARY TECHNICAL RESULTS OF NSABP-B-32

Sentinel node identification rate (Both arms, n=5,210)	97%
Percent of identified sentinel nodes that were positive (Both arms, n=5,058)	26%
SNB overall accuracy (Arm 1 only, n=2,461)	97.2% (95% CI, 96.5-97.8)
SNB negative predictive value (Arm 1 only, n=1,811)	96.1% (95% CI, 95.2-97.0)
SNB sensitivity (Arm 1 only, n=720)	90.3% (95% CI, 88.1-92.4)
SNB false-negative rate (Arm 1 only, n=720)	9.7% (95% CI, 7.6-11.9)

SNB = sentinel node biopsy

SOURCES: NCI Physician Data Query, December 2004.

Julian TB et al. Presentation. San Antonio Breast Cancer Symposium, 2004;Abstract 14.

PHASE III RANDOMIZED STUDY OF AXILLARY LYMPH NODE DISSECTION IN WOMEN WITH STAGE I OR IIA BREAST CANCER WHO HAVE A POSITIVE SENTINEL NODE

Protocol IDs: ACOSOG-Z0011, GUMC-00153
Accrual: 1,900 (Closed)

Eligibility	Stage I or IIA breast carcinoma amenable to lumpectomy with a positive sentinel node
ARM 1	Axillary lymph node dissection involving removal of at least level I and II nodes, followed by whole breast radiation therapy (exclusive of a third supraclavicular field) 5 days a week, for a maximum of 7 weeks
ARM 2	Breast radiation therapy only (as in Arm 1)

Patients in both arms may receive adjuvant systemic therapy at the discretion of the treating physician.

SOURCE: NCI Physician Data Query, January 2005.

ALMANAC TRIAL COMPARING SENTINEL NODE BIOPSY TO CONVENTIONAL AXILLARY TREATMENT IN PATIENTS WITH CLINICALLY NODE-NEGATIVE INVASIVE BREAST CANCER

Accrual: 1,031 (Closed)

Eligibility	T1-3, N0, invasive breast cancer
ARM 1	Standard axillary procedure (clearance or sampling)
ARM 2	Sentinel node biopsy → positive → radiation or surgery to axilla → negative → observation

	Standard axillary procedure	Sentinel node biopsy	*p*-value
Nodal positivity[1]	23%	26%	—
Arm swelling (patient reported)[2]*			
3 months – mild	12%	4%	<0.001†
3 months – moderate or severe	3%	1%	
6 months – mild	14%	4%	
6 months – moderate or severe	3%	0.5%	
Sensory loss (patient reported)[1]*			
1 month	62%	18%	<0.0001†
3 months	54%	20%	
6 months	43%	16%	
Sensory loss (physician assessed)[2]*			
1 month	42%	14%	<0.0001†
3 months	38%	14%	
6 months	37%	14%	
Drain usage[2]*	79%	17%	<0.001†
Mean days of hospital stay[2]*	5.4 days	4.1 days	<0.001‡
Return to normal activities in 6 months[2]*	93%	96%	<0.001‡

* Intention to treat; † Chi-square; ‡ Mann-Whitney test

SOURCES: [1] ALMANAC trialists'. Presentation. San Antonio Breast Cancer Symposium, 2004;Abstract 15.

[2] Mansel RE et al. Presentation. San Antonio Breast Cancer Symposium, 2004;Abstract 18.

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CURRENT STATUS OF SENTINEL LYMPH NODE BIOPSY

We now have clear data that sentinel lymph node biopsy is the staging procedure of choice for clinically node-negative breast cancer. Over 4,000 cases have been published with a mean follow-up of at least two years and the incidence of isolated axillary failure is one tenth of one percent, which is very low. Additionally, we now have two randomized trials evaluating the incidence of nodal positivity in women staged by sentinel node biopsy versus axillary dissection.

Sentinel node biopsy provides staging accuracy equivalent to axillary dissection, and the morbidity is clearly less — not only the immediate postoperative morbidity but also two years later in measurable differences in pain, paresthesia, arm motion and lymphedema. Additionally, we now know long-term local tumor control is good.

— Monica Morrow, MD

NSABP-B-32 SENTINEL NODE STUDY

The preliminary specificity and sensitivity data from NSABP-B-32 shows a nine to 10 percent false-negative rate for detecting positive nodes with the sentinel node resection. One can say that surgeons with more experience have a lower rate or that if we examine two or three sentinel nodes, we can lower that rate. However, if we examine four to five nodes, aren't we really talking about an axillary node dissection?

When we examined some of the older NSABP data to determine how many nodes were necessary to establish positive nodes in the axilla, the number was between six and eight. Any number of nodes below that had a high false-negative rate, while any number above that was superfluous.

I don't believe questioning the accuracy of axillary node dissection is particularly helpful. In this randomized prospective trial with over 5,500 women, the false-negative rate with sentinel node biopsy is nine to 10 percent and that's the inescapable conclusion of this trial.

— Norman Wolmark, MD

THE ALMANAC TRIAL

The ALMANAC data show a significant decrease in arm mobility problems and lymphedema with sentinel node biopsy; however, the data actually overestimate the morbidity experienced by the sentinel node group because 20 percent of those patients actually underwent axillary node dissection for a positive sentinel node or they received axillary radiation. I believe the numbers were skewed against sentinel node biopsy and that the associated morbidity is probably much lower than these data suggest, which are already much lower than the results seen in the axillary node dissection group.

— Harry D Bear, MD, PhD

I was the primary investigator for the quality of life study in the ALMANAC trial, and it was probably the first time since I've been working in this area that we've actually had quality of life as the primary endpoint in a surgical trial. In fact, anxiety was not affected and the quality-of-life benefits were superior in women who were randomly assigned to sentinel lymph node biopsy because they experienced less arm morbidity.

Another important aspect of this study is that, although physicians care deeply about their patients, often the focus of attention when reviewing clinical trial data is predominantly on life-threatening adverse events. For women actually experiencing any of our treatments — surgery, chemotherapy or hormone manipulation — non-life-threatening, but nevertheless significant, side effects can dramatically impair quality of life. Lymphedema usually doesn't kill anybody, but it definitely affects one's ability to function adequately in the home and professional world and in care-taking roles. The ALMANAC trial has at least given us clear indications that the sentinel lymph node procedure should become the standard of care.

— Lesley Fallowfield, PhD