

Targeted surgical procedures in oncology: Z1071 sentinel node protocol

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A dominant theme in cancer therapy is tailoring therapeutics based on specific tumor biology. While this may seem more relevant to systemic treatments, the concept of targeted surgical procedures is also developing. Sentinel lymph node biopsy (SLNB) is an excellent example of targeted surgical therapy. In the past, many breast cancer patients underwent axillary lymph node dissection (ALND) only to discover postoperatively that all nodes were negative for metastatic disease. For early stage breast cancer and melanoma, lymphatic mapping (LM) and SLNB are now standard procedures that identify those patients who have node positive disease and may benefit from a regional lymph node dissection.

The American College of Surgeons Oncology Group (ACOSOG) has a strong history of targeted surgical procedure trials in breast cancer. ACOSOG Z10 (5500 patients) and ACOSOG Z11 (891 patients) were two SLNB trials for early stage breast cancer.^{1,2} However, the role of LM and SLNB for locally advanced breast cancer treated with neoadjuvant chemotherapy remains controversial. Preoperative chemotherapy regimens are effective in inducing primary tumor regression, which can lead

to increased breast-conserving surgery. For example, ACOSOG Z1041 is studying neoadjuvant chemotherapy-trastuzumab regimens and preliminary data suggest a 60 percent pathologic complete response (pCR) rate at the primary tumor site.³

As systemic neoadjuvant regimens improve for locally advanced disease, surgeons are seeing greater response rates both in the primary tumor and in the axilla. Many patients who present with locally advanced breast cancer have axillary nodal metastases that are biopsy proven, using axillary ultrasonography and either fine needle aspiration (FNA) or core needle biopsy. Such nodal disease can also respond to neoadjuvant therapy. An important question is whether SLNB is sufficiently accurate to predict node negative disease throughout the axilla, following neoadjuvant therapy. The fibrosis and distorted architecture of a sentinel lymph node (SLN), which once contained metastatic disease, could impair the lymphatic drainage from the breast, and thereby alter the accuracy of LM and SLNB.

ACOSOG Z1071 is a phase II study entitled Evaluating the Role of Sentinel Lymph Node Surgery and Axillary Lymph Node Dissection Following Pre-

operative Chemotherapy in Women with Node Positive Breast Cancer T1-4, N1-2, M0 at Initial Diagnosis. The study chair is Judy Boughey, MD, FACS. This trial was activated on July 15 and is available on the ACOSOG Web site in order for ACOSOG surgical investigators to submit to their institutional review board and begin enrollment. The primary objective of the trial is to determine the false negative rate for SLN. The false negative rates are defined as the number of patients declared to have no evidence of cancer in the SLN, and are found to have at least one positive lymph in the ALND, divided by the total number of patients with at least one positive axillary lymph node by ALND. The secondary objectives include determining the following factors:

- The accuracy of axillary ultrasound in assessing nodal disease after neoadjuvant chemotherapy
- The nodal status of patients after preoperative chemotherapy
- Whether the false negative rate for SLN surgery after neoadjuvant chemotherapy is related to the extent of residual cancer overall or separately in the breast or regional node basin
- The pCR rates for both

breast and lymph nodes, and disease-free survival in node positive patients receiving neoadjuvant chemotherapy

The correlative science objective is to determine the incidence and risk factors associated with the lymphedema following ALND. The target accrual for this trial is 550 patients. The eligibility criteria for Z1071 include:

- Histologic diagnosis of invasive breast cancer.
- Clinical stage T1-4, N1-2 (non-inflammatory), M0.
- Patients must have an FNA or core needle biopsy of an axillary node documenting nodal disease at the time of diagnosis.
- Patient will receive preoperative chemotherapy.

Clinical staging criteria has been adapted from the *AJCC Cancer Staging Manual, 6th Edition, 2002*. The interventions include preoperative chemotherapy and axillary ultrasound. The preoperative chemotherapy regimen will be determined by the treating medical oncologist. After completion of neoadjuvant chemotherapy, a restaging ultrasound is required to assess the response in the breast and axilla. The site medical oncologist can use their regimen for neoadjuvant chemotherapy. Patients then proceed to surgery with LM, SLNB, and ALND and resection of the primary tumor.

ACOSOG continues to develop its portfolio of clinical trials that ask important surgical questions. Z1071 has the potential to determine the accuracy of LM and SLNB after patients have completed preoperative che-

motherapy. The vast majority of patients undergo an ALND despite clinical evidence of primary and axillary nodal disease regression. This trial could determine the value of SLNB and reduce unnecessary ALNDs, which will reduce the morbidity associated with the treatment of node positive breast cancer. Breast surgeons are encouraged to go to the ACOSOG Web site and evaluate this clinical trial for their patients.

Targeted surgery is about focusing treatment in order to reduce morbidity while controlling the disease—an important theme of many ACOSOG trials; we will continue to develop such trials in the future. We encourage you to learn more about ACOSOG by visiting <http://www.acosog.org>. You will discover that these trials address important questions that are relevant to practicing surgeons. Answers to these questions can only be obtained through our collective efforts.

We look forward to your participation in advancing the science of surgery.

References

1. Wilke LG, McCall LM, Posther KE, Whitworth PW, Reintgen DS, Leitch AM, Gabram SG, Lucci A, Cox CE, Hunt KK, Herndon JE, II, Giuliano AE. Surgical complications associated with sentinel lymph node biopsy: Results from a prospective international cooperative group trial. *Ann Surg Oncol*. 2006;13(4): 491-500.
2. Lucci A, McCall LM, Beitsch PW, Whitworth DS, Reintgen PW, Blumencranz AM, Leitch SS, Hunt KK, Giuliano AE. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. *J Clin Oncol*. 2007;25(24): 3657-3663.
3. Ota DM, Nelson H. Neoadjuvant therapy trial for HER2/neu positive breast cancer. *Bull Am Coll Surg*. 2007;92(10):63.

Trauma meetings calendar

The following continuing medical education courses in trauma are cosponsored by the American College of Surgeons Committee on Trauma and Regional Committees:

- **Disaster and Mass Casualty Management 2009**, December 10, Kansas City, MO.
- **Advances in Trauma 2009**, December 11–12, Kansas City, MO.
- **Medical Disaster Response 2010**, March 21, 2010, Las Vegas, NV.

- **Trauma, Critical Care, and Acute Care Surgery, 2010**, March 22–24, 2010, Las Vegas, NV.

- **Point/Counterpoint XXIX**, May 24–26, 2010, National Harbor, MD.

Complete course information can be viewed online (as it becomes available) through the American College of Surgeons' Web site at <http://www.facs.org/trauma/cme/traumtgs.html>, or contact the Trauma Office at 312-202-5342.