What Is the Role and Impact of the Sentinel Node Sampling Technique in Breast Cancer Staging?

Douglas Reintgen, MD

**Sentinel node sampling is a technique that can reduce the morbidity and increase the specificity of axillary node dissection.**

Lymphatic mapping and sentinel node biopsy were initially developed for nodal staging in the malignant melanoma population. Morton and colleagues developed a procedure that permits intraoperative identification of the sentinel lymph node, the first node in the lymphatic basin from which the primary tumor drains. If that sentinel node is negative for metastatic disease, the remaining nodes in the lymphatic basin are also likely to be negative.

Prior to surgery, the patient undergoes lymphoscintigraphy in which he or she is injected with a colloid tracer that identifies the lymphatic basins at risk for metastatic disease and the location of the sentinel node(s). Intraoperatively, the patient receives injections of a vital blue dye and radiocolloid around the primary tumor, which is taken up by the cutaneous lymphatics. The blue-staining lymphatics are followed to the sentinel nodes, which are then harvested and submitted to pathology. We subsequently have refined this technique by using a hand-held gamma-detection probe that measures the radiolabelled colloid injected during the lymphoscintigraphy to confirm the location of the sentinel node(s) intraoperatively.

Our initial experience with this technique in breast cancer involved 62 patients with newly diagnosed invasive breast cancer and therefore a defined rate of metastatic disease to the axilla. All patients had intact tumors, preventing any disruption of the lymphatics from a large excisional biopsy, and underwent preoperative lymphoscintigraphy and intraoperative mapping using blue dye and radiocolloid. Following sentinel node biopsy, all patients underwent either lumpectomy and axillary node dissection (63%) or a modified radical mastectomy (37%). Because we also wanted to document the incidence of skip metastasis (negative sentinel node and positive nonsentinel higher nodes) with this technique, we harvested the sentinel node and then completed the node dissection, removing a mean of 2.2 sentinel nodes and 15.5 nonsentinel nodes in each patient.

We successfully identified the sentinel node in the axilla in 57 (92%) of 62 patients. Of the 57 patients, 18 (31%) had micrometastatic disease, and the sentinel node was positive in all 18 patients. Importantly, the sentinel node was the only site of disease in 12 (67%) of the 18 patients with micrometastatic disease. We did not observe a skip metastasis. Thus, these data suggest that breast cancer patients can be nodally staged using a sentinel node biopsy procedure.

Although earlier reports describing this technique in breast cancer had limited success in identifying the sentinel node, the combination method we used with our initial 62 patients identified the sentinel node in 92% of cases, with a measurable learning curve. Thus, I believe this technique can be widely applied with less morbidity to stage the breast cancer patient.

We are now trying to address three issues: (1) the applicability of the lymphatic mapping techniques to a multicenter setting, (2) the possibility of performing accurate sentinel node mapping following excisional biopsy, and (3) evaluation of the role of a detailed pathologic sentinel node examination for better staging. We are fairly certain that we can accurately map in women with intact tumors, but many women present to us following excisional biopsy in a community hospital. We are also trying to expand the use of this procedure and have developed a program using teams of nuclear medicine physicians, pathologists, and surgeons to train other centers and the community in the use of these techniques.

Good pathology support is important to success. With this lymphatic mapping technique, the pathologist receives one or two lymph nodes for examination that are likely the first metastatic site. This allows more detailed lymph node examination and an increase in disease-staging accuracy. Applying polymerase chain reaction (PCR) techniques improves the pathology examination sensitivity by two orders of magnitude over the naked eye and routine examination. Thus, I believe these new techniques will result in more accurate staging for the breast cancer population.

This technique can also avoid the complications and morbidity that result from axillary dissection for breast cancer. Approximately 40% of women who undergo axillary dissection develop acute lymphedema or extremity swelling. In 5%, the swelling becomes chronic, and treatment is relatively limited. In addition, paresthesias develop in 40% of patients. A drain is required in all patients; after drain removal, 10% develop seromas that require further drainage. In contrast, the primary morbidity of a sentinel node biopsy is a scar that is usually hidden in the axilla. Lymphedema or seromas rarely occur.

Our eventual hope for the breast cancer population is to subgroup patients who are truly histologically node-negative. Currently, women with invasive breast cancer...
Experience in Women With Previous Excisional Biopsies

DR HORTON

What is your experience with these techniques in breast cancer patients since your initial report?

DR REINTGEN

We have performed these techniques on approximately 200 patients, including women with previous excisional biopsies. We continue to show that the sentinel node is the first metastatic site. We have documented three skip metastases in approximately 50 women in whom we have performed mapping following excisional biopsy. Therefore, in these patients we complete the node dissection following harvest of the sentinel node. The rate of skip metastases in women after excisional biopsy remains unclear. However, we are confident with the lymphatic mapping and sentinel node biopsy techniques if the tumor is intact. We have initiated an in-house protocol in which we harvest only the sentinel node in these women. If negative, we do not perform any further lymph node dissection.

Redefining Minimal Disease in the Adjuvant Setting

DR SLEDGE

If the patient has two positive cells by RT-PCR, a very important question in running a cooperative group adjuvant trial is whether that patient should be identified as having a positive axillary lymph node; it is not going to be a matter of simply identifying that patient as lymph node-negative. There will be shadings of gray in the meaning of "minimal disease" in an adjuvant setting; we simply do not yet know the answer. This is a long-term question that will require five or 10 years of follow-up on 1,000 or 2,000 patients to answer.

DR HORTOBAGYI

Clearly, the lymphatic mapping and sentinel node biopsy procedures are here to stay. Decreasing the need for axillary dissection is very positive from the patient perspective. However, like Dr Sledge, my greatest concern is the challenge of interpreting the data and the risk of stage migration. There is an enormous prognostic difference between the histologically positive PCR-positive patient and the histologically negative PCR-positive patient. By detecting the histologically negative PCR-positive patients, you will actually improve the prognosis of both the node-negative and node-positive groups. Some patients from the node-negative group will now be identified as node-positive and have a much better prognosis than patients normally identified as node-positive. Essentially, today's T1, N0 patient will differ from the T1, N0 patient in five years.

The proof will be whether there is any clinical correlation. Currently, we are treating women who are histologically negative with adjuvant cytotoxic chemotherapy, and the potential to subgroup that population is exciting. People have tried to subgroup this population based on prognostic factors related to the primary tumor. However, the metastatic cell in the regional node really is more important. Thus, if there is a potential to subgroup the histologically node-negative population, we ought to pursue this line of research.

Patient Selection

DR SLEDGE

If it is important to perform this procedure with an intact tumor (palpable or nonpalpable), how will this change our initial approach to the patient with breast cancer? For instance, currently in my institution, if a patient has a mammographic or ultrasonographic abnormality, or my radiologist suggests the patient has a 30% or 40% likelihood of having a breast cancer based on their experience, we must decide whether this patient has benign disease. In the future, will we have to perform this technique on every patient who has microcalcifications, a stellate mass, and/or a solid mass by ultrasonography? Many of those patients will have benign disease. Are we committing to performing this procedure first in everyone with a mammographic abnormality if we need an intact tumor for adequate sentinel lymph node mapping and excision?

DR REINTGEN

I believe the primary educational process in breast cancer will address how breast tumors are diagnosed. This opens the field of stereotactic biopsy because mapping is more effective with an intact tumor. Thirty patients in our initial series of 62 had mammographically detected tumors only, which indicates that their diagnoses were made with stereotactic biopsy. We are very accurate at mapping with the minimal tumor-bed disruption that occurs with a stereotactic biopsy. Thus, I believe we will be able to diagnose these patients with stereotactic biopsy.

In those women subsequently diagnosed who then require a lumpectomy, it will be possible to inject the radiocolloid and blue dye in the same site down through the tumor localization needle. There are some patients where the diagnosis of cancer cannot be made before going to the operating room. However, nothing is lost by injecting the radiocolloid in patients with a suspicion of cancer. The radioactivity injected is very low, 450 mCi. In comparison, patients receive 20 mCi with a bone scan. The mapping procedure is benign except for blue urine as a result of the dye. Therefore, even if you do not have a diagnosis and must inject the mapping agents prior to diagnosis, you expose the patient to no significant risk.

Node Sampling Requirement for Eastern Cooperative Oncology Group (ECOG) Breast Cancer Trials

DR HORTON

Dr Sledge, what specifically is ECOG doing with regard to node sampling?

DR SLEDGE
The next generation of trials starting within a few months will probably accept sentinel node sampling. The assumption of the ECOG Breast Committee is that the requirement for 10 or more studied nodes will be eliminated, particularly for those patients who are truly lymph-node-negative by sentinel lymph node biopsy.

**DR HORTON**

Clinicians and investigators use the number of involved lymph nodes as an important prognostic factor for breast cancer. When you have a positive sentinel lymph node and perform a more formal axillary lymph node dissection, how many lymph nodes do you then dissect? Do you perform a routine axillary lymph node dissection?

**DR REINTGEN**

This is a viable question to answer in a future clinical trial. Currently, all women with a positive sentinel node undergo a complete node dissection, and the resulting information is provided to the medical oncologist to make further treatment decisions.

**M.D. Anderson Experience With Lymphatic Mapping and Sentinel Node Biopsy**

**DR HORTON**

Dr Hortobagyi, what is the M.D. Anderson experience with lymphatic mapping and sentinel node biopsy?

**DR HORTOBAGYI**

The melanoma group is using this technique. In patients with breast cancer, we use ultrasound more frequently than many other centers to noninvasively evaluate the status of the axilla. To start identifying groups of patients with early-stage breast cancer who may not need an axillary dissection, we have initiated a clinical trial in which patients with stage II and III disease are treated with primary or neoadjuvant chemotherapy. Of those with demonstrated response to chemotherapy, we are currently randomizing individuals with early breast cancer who are both clinically and radiographically negative to an axillary dissection or no axillary intervention. Furthermore, we plan to participate in a multicenter trial to assess the value of sentinel node biopsy.

**References**