Invited commentary: Sentinel node biopsy—comment on techniques

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SOME ASPECTS OF THIS STUDY[1] help solidify basic concepts that are becoming apparent in the field of sentinel node biopsy for breast cancer. Blue dye injected intradermally, but in the periareolar area, with the radionuclide injected intraparenchymally around the tumor site both went to the same axillary node in 94% of their cases. Reports in the literature illustrate that a wide variety of injection sites in the affected quadrant of the breast, or even in the central subareolar area all go to the same sentinel node or nodes[2-4]; intradermal blue dye and intraparenchymal radionuclide, as in this article, or both intraparenchymal blue dye and radionuclide or intradermal radionuclide and interparenchymal blue dye all yield concurrence between blue dye and radionuclide node localization in 90% or more of cases. The infrequency of false-negative axillary nodes,[5] the percentage of positives nodes, and the general pattern in terms of the number of sentinel nodes seem to be consistent across all studies. One can confidentially conclude that the breast lymphatics are regional and not point-specific in anatomic distribution and functional physiology. Therefore, the exact location of the marker injection, whether blue dye or radionuclide, is probably not important anatomically, while there may be aspects that favor certain injection practices. For instance, in our experience, blue dye injected intraparenchymally may stain the subcutaneous tissue and skin, sometimes permanently, with a blue discoloration. A permanent blue tattooing of the skin after intradermal blue dye injection is common. This is true with the lymphazurin dye used in this country, but perhaps is not true with the patent blue dye used in Holland. When blue dye is injected into the parenchyma before the excision of the primary tumor, one loses all orientation because of the heavily stained tissue; visual detail identification is lost and removal of the primary cancer is complicated. Perhaps subareolar injection will obviate this cumbersome and messy dye injection around the primary cancer.

In our experience[6] and the experience of others,[7] the intradermal unfiltered[8] radionuclide injection has significant advantages. As the Dutch authors point out,[1] when the radionuclide is injected into the parenchyma of the upper outer breast near the primary tumor site, the radioactivity scatter frequently interfered with the ability to distinguish a sentinel node close to the breast tissue, where many sentinel nodes lie. The use of the intradermal radionuclide injection obviates this problem, since once the skin is incised and the head of the detection probe is below the skin level, there is no confusing scatter from the parenchymal injection sites or the breast, and the nodes are much more readily identified. In addition, in our experience, because of the richer lymphatic supply of the skin in contrast to the breast parenchyma, the radioactive counts of the nodes in the axilla are very high, averaging more than 4000 but sometimes as high as 30,000 counts per 10 seconds. These extremely high counts enormously simplify the identification of sentinel axillary nodes. The mean and median number of nodes in our experience does not change, nor is there any differentiated localization compared with the blue nodes; it is just that more of the radioactive material reaches and lodges in the node, and background scatter counts are negligible. Identification of the sentinel node increased significantly to 97% or 98% once we abandoned intraparenchymal injection and used intradermal radionuclide injection. In our opinion, within a fairly short period of time, the

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standard injection used to identify sentinel nodes should be intradermal radionuclide only without blue dye intraparenchymally; our group is planning to make blue dye injection optional in the near future. The authors of this report[1] acknowledge this by indicating that they do not consider a node to be a sentinel node if it is identified only by blue dye.

The authors use lymphoscintigraphy preoperatively, but then state that "ultimately the . . . count in the open axilla" is the important feature of radionuclide localization; therefore, the usefulness of the lymphoscintigram is negated except for identifying internal mammary nodes. Because internal mammary nodes, even if located by lymphoscintigraphy, are by and large not dissected, it seems that scintigraphy could be avoided. We do lymphangiograms only because the nuclear medicine department is unable to bill for radionuclide injection without a subsequent scan. Lymphangiograms are not helpful with the high radionuclide sentinel node counts resulting from intradermal injection because they are easily detected by the probe both externally on preliminary examination and after the probe head is placed beneath the skin as the sentinel node procedure begins.

The authors did not address one key contentious issue in the United States, which is how many cases a surgeon needs to be adequately skilled in performing a sentinel node biopsy. The American College of Surgeons trial mandates that a surgeon needs to perform 30 sentinel node biopsies followed by an axillary dissection to become skilled; unfortunately, that level of experience puts the procedure out of the reach of the average community surgeon. This requirement is puzzling, since in no other cancer surgery are 30 cases required before a surgeon is considered "qualified." Pancreatic resections, total gastrectomies, total thyroidectomies, etc, require a far higher level of skill and have a curative function, whereas lymph node removal is only a diagnostic and prognostic test and does not alter survival. The consequence of missing 1 or 2 sentinel nodes is minor, since, for the most part, only patients with micrometastases or minimal tumor burden in the axilla are potentially effected, and most patients have adequate decisions for adjuvant systemic therapy made on the basis of primary tumor features (size, lymph vessel invasion, poor nuclear or Bloom-Richardson grade, aneuploid, high s-phase, etc).[9] With the very high axillary nodal radionuclide counts that result from intradermal injection, the procedure has become greatly simplified and almost completely reliable in our hands and in other reports[6,7] and obviates the need for extensive training.

The authors' cautionary note that the axilla should be palpated during the procedure and suspicious nodes removed in addition to the sentinel node is an excellent one, since in our experience palpable metastatic nodes—either before or during sentinel node biopsy—are the cause of most failed sentinel node biopsy procedures, presumably because of blocked and altered lymphatic flow. It is important to re-emphasize that sentinel node biopsy is a technique to find nonpalpable and occult lymph node metastases, not to reconfirm the obvious.

In their article, the authors describe 2 patients who had focal areas of increased radioactivity over the sternum, suggesting drainage to internal mammary nodes. Both of these patients had axillary node metastases. Were the axillary metastases macrometastases, suggesting secondary drainage to the internal mammary chain only? Did these patients have inner quadrant lesions? Should further studies have been done to document the enlargement of these internal mammary nodes that might harbor metastases? Since this drainage pattern was only observed in 2 patients, it may be premature to draw any conclusions.

One of the most important issues resulting from the practice of sentinel node biopsy is the understanding of lymph node micrometastases. All reports note that multiple histologic sections of 1 or 2 nodes, rather than the traditional single section of the entire axillary dissection of 16 nodes, may be more accurate in this new era of small mammographically discovered cancers. Recent reports[10] suggest that there is a worse prognosis associated with even a single micrometastasis, which earlier reports did not find. In the most recent report from the Ludwig trial,[11] the finding of a single micrometastasis in a single node by more extensive pathologic examination decreased survival by approximately 50%. The magnitude of this worsened prognosis was greater than that by changing from negative nodes to 1 to 3 macroscopically positive nodes or from 1 to 3 positive nodes to 4 or more node metastases and is therefore biologically implausible. While the reduction in mortality is statistically significant in their report, the lack of biologic plausibility should make us cautious in accepting their conclusion based on only a few (20) cases. In addition, Page et al's[12] response to a proposal by Hermanek and colleagues[13] to reclassify the AJCC Staging System to accommodate the discrepancy between true micrometastasis and clusters or individual tumor cells that may be merely passing through the node should be recognized. This is yet another situation where our technology has outstripped our understanding; further information

needs to be accumulated before we can appreciate the true prognostic implication of a micrometastasis or isolated tumor cells or a cluster of cells detected by immunohistologic staining. Much of the current sentinel node literature lumps these categories together, but it may well be that isolated circulating tumor cells or a cluster of cells less than a defined size, such as 0.2 mm as proposed by Nasser et al,[14] will be found not to have any prognostic implication. In addition, this intense histologic examination has provided a classic example of the "Will Rogers" effect—new diagnostic technologies merely stage shift patients without altering overall outcome.

The last issue the authors address concerns the nature of lymph node metastases. It is clear from many trials in melanoma and breast, gastric, head and neck, and colorectal cancers that lymph node metastases are "indicators, not governors" of prognosis and survival.[15] These studies demonstrate essentially the same survival, whether lymph nodes are removed, radiated, or observed. Thus, while the authors were able to eliminate axillary dissection in 63% of their patients by finding negative sentinel nodes, there may also be little justification for performing an axillary dissection in patients with a micrometastasis or even macrometastases. That was the lesson of the NSABP B-04 trial[16] and several other prospective trials in breast cancer that compared variations of regional lymph node treatments. Only 4 out of the authors' 18 patients with sentinel node micrometastases had other nonsentinel node metastases, all of which apparently were further micrometastases. Thus, in the move toward the worthy goal of eliminating the morbidity of axillary dissection,[17] which is only a diagnostic procedure in breast cancer patients, those with micrometastases in the sentinel nodes should also not have an axillary dissection. Seventy-five percent to 80% of contemporary patients with breast cancer could avoid axillary dissection without alterations in understanding the prognosis, selecting adjuvant treatment, or risking failure in the axilla.

Rahusen et al[1] define again the validity of the sentinel node concept and emphasize the basic principles of both lymph node anatomy, physiology, and function in the surgical management of breast cancer. This report nicely dovetails with numerous other studies of sentinel node biopsy procedures and increases our understanding of this important new prognostic technique that will allow us to simplify breast cancer surgery in the great majority of patients with breast cancer by eliminating axillary dissection and permitting outpatient management with the patient under local anesthesia, with or without conscious sedation.

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