INVITED COMMENTARY

Let Every Node Count!

Sentinel lymph node biopsy has excited the medical community and has been described by some as the most significant advance in surgical oncology in the decade of the 1990s. The technique allows accurate lymph node staging with minimum morbidity and has been successfully applied to melanoma (*1*,*2*), breast cancer (*3*,*4*), and an expanding list of other solid cancers that show significant metastatic spread to regional lymph nodes. The best results for melanoma and breast cancer are achieved when three approaches are combined to locate and remove the sentinel node. These are preoperative lymphoscintigraphy, blue dye injection at the time of surgery, and the intraoperative use of a γ-detecting probe to aid in the surgical location of the sentinel node. Success thus relies on the development of a close working relationship between the nuclear medicine physician and the surgeon. Although this requires a considerable commitment on the part of the nuclear medicine physician, it should not be seen as a chore but, rather, embraced as an opportunity to be involved in an evolving technique, the results of which impact directly on patient management. A similar level of cooperative involvement is also required from the histopathologist to ensure that the sentinel node is subjected to appropriate scrutiny using serial sections and special staining technique (*5*).

The aim of preoperative lymphoscintigraphy is to accurately map the pattern of lymphatic drainage from the primary tumor site to its draining lymph nodes. Any lymph node that receives direct lymphatic drainage from the primary tumor site is a sentinel node and should be biopsied as part of a sentinel node biopsy procedure (*6*). There must be detectable counts in the node at the time of surgery so that a γ-detecting probe can be used, and thus the radiocolloid used for lymphoscintigraphy must adequately radiolabel the sentinel node.

Therefore, successful preoperative lymphoscintigraphy requires the use of a tracer that readily enters the initial lymphatic capillary at the site of the primary tumor, moves freely through the lymphatic collecting vessels, and is retained in the sentinel node long enough for that node to be detected using a γ probe at surgery. The ideal tracer for this purpose would have close to 100% of the injected dose migrate from the primary site to the draining sentinel node and have 100% retention in that node. None of the radiopharmaceuticals in current clinical use come close to this ideal. Radiocolloids are the most common tracers used for preoperative lymphoscintigraphy and sentinel node biopsy at this time, and considerable disagreement about the particle size that is the most desirable in different clinical situations remains. Some argue that small particles more easily enter the initial lymphatic capillary and thus better radiolabel the sentinel node, whereas others argue that large particles are better because fewer second-tier nodes are radiolabeled. What does seem clear is that the search for a better tracer for sentinel node biopsy should be encouraged.

The article by Phillips et al. (*7*) in this issue of *The Journal of Nuclear Medicine* is an interesting approach to the dual problems of ensuring greater migration of tracer from the injection site while at the same time increasing retention in the sentinel node. Using their biotin-liposome/avidin technique increased retention of liposomes in the draining lymph node by a factor of 8.5 compared with that of control liposomes. This is a significant advance; nevertheless, only one in five labeled liposomes that reached the sentinel node was retained in it, which offers hope for improvement in their results. This finding is itself interesting because most radiocolloid particles that reach a sentinel node are retained by the node regardless of particle size. Perhaps the process of phagocytosis that traps radiocolloids in the subcapsular sinus of sentinel nodes is not the same process that causes the retention of liposomes.

Other attempts to improve uptake of tracer in the sentinel lymph nodes have been made. Vera et al. (*8*) used a nonparticulate receptor-binding radiotracer that combined the advantages of nonparticulate tracers (i.e., rapid entry into the lymphatic capillaries and easy movement through the lymph vessels) with the advantages of radiocolloids (i.e., good retention in the draining sentinel node). Moghimi et al. (*9*) described the use of copolymers to sterically stabilize nanospheres. This markedly increased the percentage injected dose that reached and was retained in the sentinel lymph node. They reported up to 40% of the injected dose being retained in the sentinel node, which was apparently associated with a marked increase in the rate of opsonization of the labeled nanospheres and a subsequent increase in phagocytosis by the macrophages in the subcapsular sinus of the sentinel nodes. Despite the promise of these approaches, neither appears to have been pursued further in clinical practice.

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The current methods of sentinel node biopsy do locate the sentinel nodes in most patients, and the nodes found do accurately stage the node field in >95% of patients. Nevertheless, further research into radiotracers for sentinel node biopsy should be encouraged. However, for any new tracer to be accepted by nuclear medicine physicians and surgeons it should be simple to use in clinical practice and not difficult to prepare in the nuclear medicine department. The method will need to be robust because sentinel node biopsy is now so widely applied throughout the surgical oncology community that any method that works only in a teaching hospital environment will not be adopted.

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