

# Blue Dye and $^{99m}\text{Tc}$ -Labeled Human Serum Albumin: Sentinel Node Detection by Magic Bullets?

**I**n this issue of *The Journal of Nuclear Medicine*, Bedrosian et al. (1) compare the efficacy of sentinel lymph node (SLN) biopsy using  $^{99m}\text{Tc}$ -human serum albumin (HSA) to SLN biopsy using filtered  $^{99m}\text{Tc}$ -sulfur colloid (SC). Lymphazurin blue dye is used as the gold standard of concordance for identifying the true SLN. The experimental design is a nonrandomized observational study, which demonstrates that the smaller labeled macromolecule,  $^{99m}\text{Tc}$ -HSA, is as accurate as  $^{99m}\text{Tc}$ -SC. There are several important points that deserve comment.

The study by Bedrosian et al. (1) is an empirical demonstration that  $^{99m}\text{Tc}$ -HSA consistently allows identification of the SLN when combined with blue dye. The 93% detection rate is similar to that in studies (2–4) using  $^{99m}\text{Tc}$ -SC as the radiotracer. An additional observation by Bedrosian et al. suggests that fewer “nontrue” SLNs may be obtained with  $^{99m}\text{Tc}$ -HSA, thus leading to less dissection of unnecessary draining basins and other lymph nodes. Although the incidence of micrometastasis was statistically similar for  $^{99m}\text{Tc}$ -HSA and  $^{99m}\text{Tc}$ -SC, the concordance of hot and blue node was significantly higher for the  $^{99m}\text{Tc}$ -labeled macromolecule,  $^{99m}\text{Tc}$ -HSA.

The issue of concordance raises several questions. We know from previous studies (3,4) that the success in identifying the SLN is significantly en-

hanced by the addition of gamma probe use to blue dye. In the study by Bedrosian et al., the detection of the SLN rose from only 75% using blue dye alone to 95% when blue dye was combined with gamma-probe detection; other studies have shown similar increases. This increase in detection may be attributed in part to the probe “uncovering” an otherwise unrecognized blue node, but it may also be detecting the SLN that simply has not taken up the blue dye for whatever reason. Therefore, complete concordance between radiotracer uptake and blue dye presentation may not be necessary. We must assume from the literature that the radiotracer occasionally will detect an SLN not detected with blue dye and vice versa. The same becomes true for additional lymphatic draining basins. Bedrosian et al. do not disclose the differences in the number of draining basins found between the two radiotracers. Ninety-one patients had only one draining basin, but were these equally divided between the  $^{99m}\text{Tc}$ -HSA and  $^{99m}\text{Tc}$ -SC patients, or were more single basins found in the  $^{99m}\text{Tc}$ -HSA group? This issue was addressed in 7 patients found to drain to the axilla bilaterally.  $^{99m}\text{Tc}$ -SC led to opposite axillary dissections in 3 patients with the finding of radiolabeled but nonblue-staining nodes, suggesting “nontrue” SLN detection.  $^{99m}\text{Tc}$ -HSA led to opposite axillary dissections in 4 patients, of whom 2 had complete concordance between blue and radiotracer and 2 had no SLN revealed at all. Because all positive lymph nodes in their study were blue stained, Bedrosian et al. conclude that many of these extra basins are not true SLN basins.

This is an interesting concept and one that would lead to less dissection if valid basins were accurately identified. However, without sensitivity data specifically evaluating the “hot” nonblue lymph node, one cannot discount these nodes. In our practice at the University of California at San Diego, we too have never had a nonblue “hot” node in a second draining basin be positive for metastatic melanoma. So we may be identifying more basins than are significant. But again, completion lymphadenectomy studies for these second basins in which radiolabeled nodes are found is necessary before we can discount these nodes.

The fact that  $^{99m}\text{Tc}$ -HSA provided successful SNL detection argues for a binding mechanism within lymphoid tissue. Indeed, there are quantitative studies (5,6) that support weak lymph node affinity for  $^{99m}\text{Tc}$ -HSA. Bedrosian et al. refer to an unpublished demonstration of immune-based uptake of albumin conjugated with a fluorescent dye. An established biochemical mechanism for albumin or dye binding to lymphoid tissue would be an important step toward an understanding of SLNs and the design of future SLN radiotracers.

Finally, the authors raise an interesting issue regarding the concept of an SLN. We have viewed it as being the first node draining in a given anatomic area—almost the same as the first connection in the pipes of a plumbing system. However, they suggest that the SLN may have unique properties that differ from just being the first node. Their hypothesis that there may exist antigen-presenting cells in the SLN is speculative, and the leap that a smaller tracer particle may allow selective up-

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take by the SLN will require a great deal more laboratory investigation before final conclusions can be made. However, we have all had cases in which one proximal node is very hot, followed by no radioactivity, followed by another one or two very hot nodes much more distally. Why would all the nodes in between not show uptake if the lymphatic drainage were purely plumbing? More research is needed in the study of the actual SLN. But for the purposes of this article, it raises interesting, but inconclusive, questions. Are blue dye and  $^{99m}\text{Tc}$ -labeled HSA magic

bullets to SLNs? Only time and data will answer this intriguing question.

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