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Editorial

Will the True Sentinel Node Please Stand?

Donald L. Morton, MD and Peter J. Bostick, MD

Since our original description in 1990 of intraoperative lymphatic mapping and sentinel lymphadenectomy (SLND) for patients with primary cutaneous melanoma,[1,2] over 250 articles have been published on this subject. Currently, we are conducting a Phase III international multicenter trial of lymphatic mapping and SLND to determine if there is a survival advantage for melanoma patients undergoing wide local excision (WLE) and SLND versus WLE alone ("A Clinical Study of Wide Excision Alone Versus Wide Excision with Intraoperative Lymphatic Mapping and Selective Lymph Node Dissection in the Treatment of Patients with Cutaneous Invasive Melanoma"; D. L. Morton, Principal Investigator). In the very near future, the American College of Surgeons will be conducting a trial of intraoperative lymphatic mapping and SLND for patients with early breast cancer, to determine if this technique can replace axillary lymph node dissection for breast-conserving therapy. The national and international interest aroused by SLND over the past 8 years suggests that this very simple concept might revolutionize the management of melanoma and many other, more common solid neoplasms.[3]

In this issue of *Annals of Surgical Oncology*, Tafra and associates[4] use an animal model of intraoperative mapping with two different particle sizes of the same radiopharmaceutical agent to illustrate the difficulty in defining the sentinel node (SN) on the basis of radioactive counts. This innovative study demonstrated that filtered sulfur colloid identified more "hot" nodes (possibly SN) than did unfiltered colloid. It is our view that the number of hot nodes will vary with the radiopharmaceutical and with the interval between its injection and the surgical procedure, because these agents continue their flow up the chain of lymph nodes as time elapses. Thus, the definition of the SN will always be somewhat ambiguous when lymphatic mapping is performed with radiopharmaceuticals alone. The SN should be among the hot nodes if all hot nodes are removed—but not all hot nodes are SN! Therefore, before proceeding any further, we must be very clear on the definition of the SN.

The SN is the first draining lymph node on the direct lymphatic drainage pathway from the primary tumor site. Therefore, it is the node most likely to receive metastases from the primary tumor.[1,2] Before starting our clinical studies of dye-directed SLND, we rigorously assessed the intralymphatic kinetics of various vital dyes in a feline model.[5] Patent blue-V and isosulfan blue dyes were the best agents for identifying the regional lymphatic drainage patterns. When injected intradermally, they rapidly entered the lymphatics with minimal diffusion into surrounding soft tissue. Their bright blue color was readily visible and allowed easy identification of the lymphatic channel. Elevation of skin flaps before injection of the tracking dye allowed us to observe the rapid uptake and progress of the dye along the lymphatics into the SN. The other dyes we studied proved to be unsatisfactory and were abandoned, largely because rapid diffusion into the surrounding tissue and insufficient retention by the lymphatic vessels left too little dye to reach and stain the SN.

When intraoperative lymphatic mapping is performed with isosulfan or patent blue dye, the SN is identified by following a blue-stained lymphatic channel draining from the primary tumor site to a blue-stained node (the SN). In our initial studies while developing the technique, three surgeons who had varying experience with dye-directed mapping identified a blue-stained SN in 82% of lymphatic basins overall, and the most experienced surgeon had a success rate of 96%.[2] After establishing the technique, we successfully identified the SN in 90% of patients with early-stage melanomas in the head and neck region draining to the parotid or neck, an anatomic site that has a relatively complex lymphatic

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From the Roy E. Coats Research Laboratories of the John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, CA 90404.

Address correspondence and reprint requests to: Dr. Donald L. Morton, John Wayne Cancer Institute, 2200 Santa Monica Boulevard, Santa Monica, CA 90404. Phone: 310-829-8781; Fax: 310-582-7185.

drainage pattern.[6] In our most recent series, we used isosulfan blue dye to identify a blue-stained SN in 92% of 100 lymphatic basins.[7] Although there is a shallow learning curve for intraoperative mapping performed using blue dye alone, others have confirmed our findings.[8–10]

In January of 1993, we began to investigate the addition of intraoperative radiolymphoscintigraphy for intraoperative lymphatic mapping of the SN. At the March 1994 meeting of the Society of Surgical Oncology, we presented the concept of using blue dye in conjunction with radiopharmaceuticals to increase the technique's accuracy and increase the slope of its learning curve.[11] However, the intralymphatic kinetics of radiopharmaceutical agents has not been established. One reason is that investigators continue to perform intraoperative mapping while using a wide variety of radiopharmaceutical agents: human serum albumin, albumin colloid, sulfur colloid, trisulfide colloid, and stannous phytate. Also, there is considerable variation in the interval between radiopharmaceutical injection and SLND, ranging from no delay to greater than 24 hours. We have shown that this can dramatically influence the number of hot nodes as the radiopharmaceutical agent passes up the chain of lymph nodes.[12] Moreover, as demonstrated by Tafra et al.[4] in their porcine model, the number of SN and the radioactive counts measured over the SN depend on whether the radiopharmaceutical agent is filtered. In their study, almost twice as many hot nodes with 2-fold higher radioactive counts were excised with filtered sulfur colloid. As pointed out by Tafra et al.,[4] it is not clear whether these additional hot nodes represent true SN. Finally, other variables such as the amount of radiopharmaceutical injected and the distance between the dissected basin and the primary site will affect the radioactive counts measured over the SN.

The result of all these variations is an alarmingly disparate set of definitions: an SN has been defined by a radioactive count of 10-25 in 10 seconds,[13] a count of 300-3000 in 10 seconds,[14] an in-vivo node to background count ratio ≥ 2 or 3,[15] or an ex-vivo sentinel to nonsentinel node count ratio >10.[7] Each of these definitions is arbitrary and subject to our limited knowledge of the intralymphatic kinetics of particular radiopharmaceutical agents. Moreover, we have demonstrated that the SN is not necessarily the "hottest" node in the lymphatic basin,[16] although 92% of the time it will be among the hot nodes.

Since only the blue dye can identify the afferent lymphatic channels leading to the SN, blue dye must remain the unambiguous gold standard for identifying the true SN. However, we believe that dye-directed and probe-directed techniques for mapping the path to the SN are complementary and should be used together. In our most recent series, we identified the SN in 98% of lymphatic basins using both blue dye and a radiopharmaceutical agent.[7] Only 6% of SN were identified with the probe alone, and none of these contained micrometastases; in contrast, 8% of SN were blue but not hot and, more importantly, some of these blue nodes contained micrometastases. While other institutions report a similar success rate, the range of basins in which the SN is hot but not blue varies from 20%-40%.[17] In the animal model reported by Tafra and associates,[4] 33% of SN were hot but not blue when mapped by filtered sulfur colloid. Because of the nonstandard definition of an SN identified by radiopharmaceutical agents alone, the true SN may have been only the blue nodes or the true SN may not have been removed!

Our current method for intraoperative lymphatic mapping and SLND is as follows:

1. Preoperative lymphoscintigraphy using filtered Tc-99m sulfur colloid is performed for all patients undergoing intraoperative lymphatic mapping and SLND.
2. The blue dye is injected 5-15 minutes before intraoperative lymphatic mapping and SLND. Filtered Tc-99m sulfur colloid may be reinjected if more than 24 hours has passed since preoperative lymphoscintigraphy.
3. The SN is identified by a blue-stained afferent lymphatic channel leading from the primary tumor to the blue-stained node. The gamma probe is used as an adjunct in guiding the surgeon to the first blue-stained SN and identifying additional blue-stained SN when the basin counts do not drop to background levels after removal of the first blue/hot node.
4. If the blue-stained SN cannot be identified, hot nodes with an in-vivo or ex-vivo to background count ratio ≥ 2 are removed. All nodes should be excised until the basin count ratio is <2 times background.

Based upon our limited knowledge of the intralymphatic kinetics of radiopharmaceutical agents, we must conclude that the first draining lymph node from the primary tumor site and the first site of any nodal metastases is the *blue-stained* SN. Cutaneous lymphoscintigraphy and the gamma probe should be used to guide the surgeon to this blue-stained SN.

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