Ann Surg Oncol (2011) 18:3232–3234
DOI 10.1245/s10434-011-1996-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL

What is the Significance of the In Transit or Interval Sentinel Node in Melanoma?

Jonathan S. Zager, MD, Christopher A. Puleo, PA-C, and Vernon K. Sondak, MD

Department of Cutaneous Oncology, Moffitt Cancer Center, Tampa, FL

The advent of radionuclide lymphoscintigraphy as part of sentinel lymph node biopsy procedures for melanoma led to changes in our understanding of lymphatic anatomy, but the clinical significance of these changes are still undefined. Although it quickly became clear that primary melanomas frequently drained to lymph nodes outside of the traditional "major" basins (cervical, axillary, and ilioinguinal), it has been less clear what to do about these nodes—or even what to call them. Definitions of the three major nodal basins and their subdivisions are fairly standardized: the axillary basin consists of levels I–III; the ilioinguinal basin can be broken down into inguinofemoral, external, and common iliac and obturator nodes; and the cervical basin consists of levels I–VI. Whether to include occipital, pre- and postauricular, and parotid nodes as part of the cervical basin has not been totally standardized, but it seems reasonable to include them. For the extremities, epitrochlear and popliteal nodes are considered "minor" nodal basins, and internal mammary nodes often are but not always classified similarly (but probably should be). Beyond that, there is little standardization about what to call the many nodes that can be found in small numbers throughout the body, especially in the soft tissues of the posterior and lateral trunk, which occasionally serve as primary draining nodes for the skin.

We propose the following lexicon: interval nodes are any superficial (i.e., outside the chest and abdominal cavities) lymph nodes identified by conventional or single photon emission computed tomography (SPECT) lymphoscintigraphy, other imaging studies, incidentally at surgery, or clinically based on involvement with tumor that are not located within the defined confines of a major or minor nodal basin. (This definition is similar to but subtly different than that by Verwer et al. in this issue of *Annals of Surgical Oncology*.[1]) This definition includes nodes within the soft tissues of the scalp, by the tip of scapula, in the triangular muscular space or biceps groove, along the saphenous vein but outside the femoral triangle, at the costal margins (especially below the 11th and 12th ribs), and alongside breast tissue and in the lateral axillary line but outside the confines of the axilla. In contrast (and in keeping with the definition of intralymphatic but extranodal metastases), *in transit* nodes are any nodes located between a primary cutaneous malignancy and the major basin(s) traditionally considered to drain that site. This definition would thereby encompass both interval and minor basin nodes or any nodes that would not be removed by performing a standardized regional lymphadenectomy. At the present time, including the study by Verwer et al.,[1] there is no clinical basis to believe the biology of interval and minor basin nodes differ in terms of their likelihood of involvement by cutaneous melanoma or (perhaps more importantly) in their status as predictors of tumor involvement of major basin nodes. Because the clinical management considerations are essentially the same for interval and minor basin nodes, it makes sense to consider them together as in transit nodes.

One shortcoming of this definition is how to account for direct drainage from a primary cutaneous melanoma to retroperitoneal, mediastinal, para-aortic, or paravertebral nodes? Fortunately this rarely happens, and importantly these nodes are almost never successfully harvested by sentinel node biopsy. Moreover, drainage to these areas is virtually always "terminal" (no efferent lymphatic to a major basin node; Fig. 1a) as opposed to "in transit" to the axilla or groin. When these nodes are identified by

First Received: 6 July 2011;
Published Online: 12 August 2011

J. S. Zager, MD
e-mail: jonathan.zager@moffitt.org

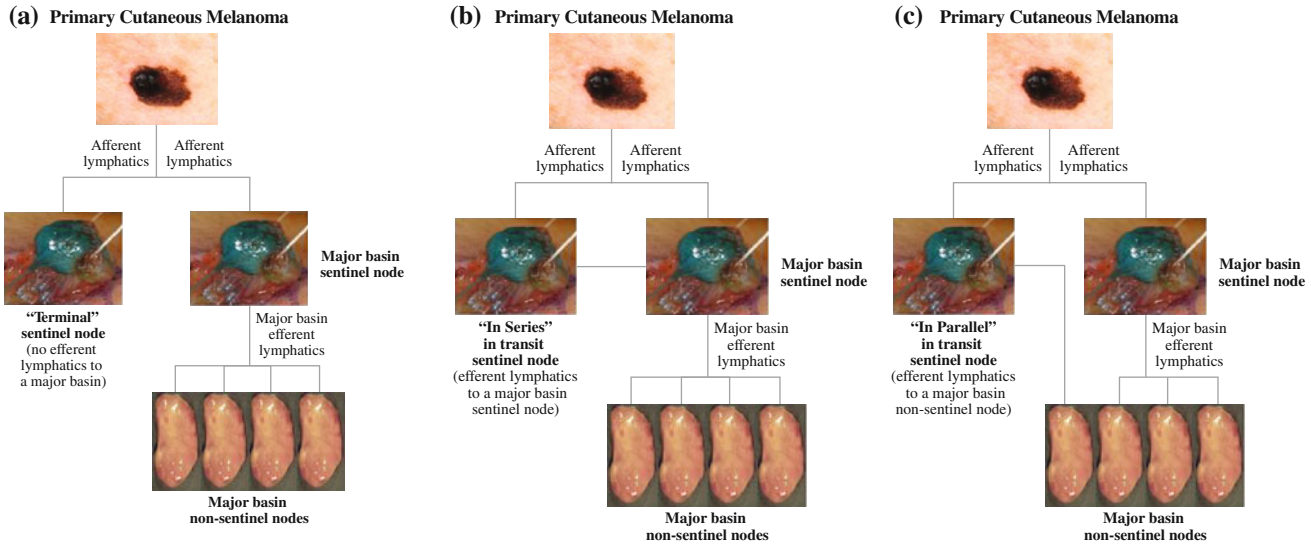

FIG. 1 Potential drainage pathways for sentinel lymph nodes situated outside of major basins and their clinical implications. **a** "Terminal" nodes are nodes that receive afferent lymphatics from a cutaneous primary but do not have efferent lymphatics to a major basin; no regional lymphadenectomy would be indicated whether a terminal sentinel node contains tumor. **b** "In series" nodes receive afferent lymphatics from a cutaneous primary and send efferent lymphatics to a sentinel node in the major basin; if the major basin sentinel node is negative, no regional lymphadenectomy would be indicated even if the in transit sentinel node contains tumor. **c** "In parallel" nodes receive afferent lymphatics from a cutaneous primary but send efferent lymphatics to a nonsentinel node in the major basin; if a major basin sentinel node is negative, there would still be a substantial risk of metastatic disease within that major basin and lymphadenectomy would be appropriate to consider

preoperative lymphoscintigraphy, postoperative surveillance is indicated without direct surgical or nonsurgical treatment.

Important questions remain regarding in transit nodes in clinically node-negative cutaneous melanoma. Are particular agents or lymphoscintigraphy techniques better than others in helping to identify these nodes before SLN biopsy? Verwer et al. suggest that their 9% incidence of interval nodes (using a more restrictive definition of interval nodes than we have proposed) is higher than that reported in the literature because of their use of antimony trisulfide (10–15 nanometer diameter versus 50–200 nanometer diameter of sulfur colloid) as a mapping agent and "super high-resolution collimators" for scanning.[1] Antimony trisulfide is unlikely to be available outside Australia in the foreseeable future, but the small particle-size lymphoscintigraphy agent, tilmanocept,[2] has been evaluated in two phase III trials and could become available soon. As yet, there is no evidence that this agent is associated with more frequent identification of in transit nodes. Other contemporary publications describe various rates of identification of interval or in transit nodes, from 2.1% to 9.8%,[3,4] so it is not clear to what extent the Australian experience is truly outside the norm. We have, however, found SPECT lymphoscintigraphy to be very valuable for localizing in transit nodes and planning the operative approach (or occasionally deciding that the risks of removal outweighed the benefits). Whenever possible, SPECT lymphoscintigraphy should be used for patients considered at risk for in transit nodal drainage, or those suspected of having such drainage upon standard lymphoscintigraphy.

What do we do when we identify an in transit node by preoperative lymphoscintigraphy? Almost all surgeons would agree that, if the node is readily localizable, it should be excised because it represents true primary drainage from the cutaneous melanoma and identification of spread of disease to these nodes has prognostic and therapeutic implications. Reported rates of metastatic involvement of in transit nodes vary from 8%[1] to 38%,[3] likely reflecting differences among the patient populations studied and how the nodes were analyzed. For instance, Uren et al. identified interval nodes in 7.2% of all patients with melanoma who had lymphoscintigraphy but excised only 21 of these nodes and had a 14% positivity rate.[5] McMasters et al. analyzed the Sunbelt Melanoma Trial database, which included patients aged 18–70 years with melanomas at least 1.0 mm in thickness, and included any node outside of a recognized major nodal basin (in transit nodes by our proposed convention). They identified 62 of 2,332 patients (3.1%) with in transit nodes, with 21% positive for micrometastatic disease.[6] Data from our own institution showed 75 of 1,172 patients (6%) had in transit nodes identified and 12 of these patients (16%) had micrometastatic disease in these nodes.[7] The Sydney group has consistently found that metastatic involvement was less

frequent in interval and minor basin nodes than major basin nodes,[1,8,9] but the reported rates of tumor involvement are clearly high enough to justify excising and analyzing in transit nodes whenever feasible. Based on available data, a positive interval or minor basin node seems to have essentially the same impact on prognosis as a positive major basin node.

The most controversial issue remains about what to do with the upstream major basin in patients with a positive in transit node. In the Sunbelt Melanoma Trial study, 85% of the patients with positive in transit nodes had no other identifiable nodal disease, and the authors suggested that if there is a negative sentinel node in the major nodal basin a dissection of that basin may not be necessary.[6] The report by Verwer et al. agrees with this principle. In their study, of the 16 patients with positive interval sentinel nodes, 4 had negative upstream major basin sentinel nodes and no further disease identified upon completion lymphadenectomy.[1] The available data, however, by no means conclusively support that approach, and the failure rate in major basins in patients staged as in transit node-positive/major basin node-negative has not been established.

Why would one consider a complete lymphadenectomy for a patient who is in transit node-positive/major basin node-negative? Well, why do we consider a complete lymphadenectomy for a patient who has one of two positive sentinel nodes *in the same basin*? Did the finding of a second negative sentinel node somehow eliminate the need for completion lymphadenectomy? Does the first sentinel node drain to the second sentinel node in that basin or to different second-echelon nodes in the basin? In fact, anatomical considerations should drive the discussion regarding completion lymphadenectomy for positive in transit sentinel nodes. If the lymphatic drainage is in series, meaning that the in transit node(s) all drain to the same "sentinel" node in the major basin (as depicted in Fig. 1b), then indeed a negative major basin sentinel node should stage the basin adequately and lymphadenectomy would be unnecessary. But if the in transit node has second-echelon drainage via efferent lymphatics that are different from the afferent lymphatics connecting the primary site to the major basin sentinel node (Fig. 1c), then the argument that a negative major basin node eliminates the need for lymphadenectomy seems irrational. Further anatomical studies—combined with careful prospective clinical evaluation of patients with tumor-involved in transit sentinel nodes—are clearly needed.

Sentinel lymph nodes outside a major nodal basin represent a challenge both intraoperatively and postoperatively. These nodes should be biopsied if possible, but treatment algorithms are not standardized for patients with a positive in transit sentinel node. At present, we believe that management of a positive in transit node associated with negative sentinel nodes in the upstream basin(s) should be individualized based on the lymphoscintigraphic pattern of drainage as well as the estimated risk of involved non-sentinel nodes. In carefully selected patients, following the major basin with serial physical examination and ultrasonography can be readily justified. Like all clinical decision-making where lymphatics are concerned, "anatomy is destiny." The better we understand the anatomy of lymphatic drainage outside major basins, the more likely we will avoid over- or undertreating our patients with cutaneous melanoma.

REFERENCES

1. Verwer N, Scolyer R, Uren R, et al. Treatment and prognostic significance of positive interval sentinel nodes in patients with primary cutaneous melanoma. *Ann Surg Oncol.* 2011; doi: 10.1245/s10434-011-1988-5.
2. Leong SPL, Kim J, Ross M, et al. A phase 2 study of 99mTc-tilmanocept in the detection of sentinel lymph nodes in melanoma and breast cancer. *Ann Surg Oncol.* 2011;18:961–9.
3. Carling T, Pan D, Ariyan S, Narayan D, Truini C. Diagnosis and treatment of interval sentinel lymph nodes in patients with cutaneous melanoma. *Plast Reconstr Surg.* 2007;119:907–13.
4. Vidal-Sicart S, Pons F, Fuertes S, et al. Is the identification of in-transit sentinel lymph nodes in malignant melanoma patients really necessary? *Eur J Nucl Med Mol Imaging.* 2004;31:945–9.
5. Uren R, Howman-Giles R, Thompson JF, et al. Interval nodes: the forgotten sentinel nodes in patients with melanoma. *Arch Surg.* 2000;135:1168–72.
6. McMasters KM, Chao C, Wong SL, et al. Interval sentinel lymph nodes in melanoma. *Arch Surg.* 2002;137:543–7.
7. Puleo CA, Sondak VK, Cruse CW, Berman CG, Zager JS, Messina JL. Melanoma sentinel node metastases in non-traditional sites. In: Proceedings fifth biennial international sentinel node society conference, November 1–4, 2006; p. 127.
8. Hunt JA, Thompson JF, Uren RF, Howman-Giles R, Harman CR. Epitrochlear lymph nodes as a site of melanoma metastasis. *Ann Surg Oncol.* 1998;5:248–52.
9. Thompson JF, Hunt JA, Culjak G, Uren RF, Howman-Giles R, Harman CR. Popliteal lymph node metastasis from primary cutaneous melanoma. *Eur J Surg Oncol.* 2000;26:172–6.