Interval Nodes

The Forgotten Sentinel Nodes in Patients With Melanoma

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Background: Any sentinel lymph node that receives lymph drainage directly from a primary melanoma site, regardless of its location, may contain metastatic disease. This is true even if the sentinel node does not lie in a recognized node field. Interval (in-transit) nodes that lie along the course of a lymphatic vessel between a primary melanoma site and a recognized node field are sometimes seen during lymphatic mapping for sentinel node biopsy. If drainage to such interval nodes is ignored by the surgeon during sentinel node biopsy, metastatic melanoma will be missed in some patients.

Hypothesis: When lymph drains directly from a cutaneous melanoma site to an interval node, that sentinel node has the same chance of harboring micrometastatic disease as a sentinel node in a recognized node field.

Design: Preoperative lymphoscintigraphy with technetiumTc 99m antimony trisulfide colloid was performed to define lymphatic drainage patterns and, since 1992, to locate the sentinel lymph nodes for surgical biopsy or for permanent skin marking of their location with point tattoos.

Setting: Melanoma unit of a university teaching hospital.

Patients: A total of 2045 patients with cutaneous melanoma were studied in 13 years.

Results: Interval nodes were found in 148 patients (7.2%). The incidence of interval nodes varied with the site of the primary melanoma. Interval nodes were more common with melanomas on the trunk than with those on the lower limbs. Micrometastatic disease was found in 14% of interval nodes that underwent biopsy as sentinel nodes. This incidence is similar to that found in sentinel nodes located in recognized node fields, confirming the potential clinical importance of interval nodes.

Conclusions: Interval nodes should be removed surgically along with any additional sentinel nodes in standard node fields if the sentinel node biopsy procedure is to be complete. In some patients, an interval node will be the only lymph node that contains metastatic disease.

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In patients with melanoma, biopsy of sentinel lymph nodes can accurately determine their nodal status1-3 and thus avoid unnecessary further surgery when histological findings are negative. Lymphatic mapping using cutaneous lymphoscintigraphy (LS) is useful to locate sentinel lymph nodes before surgery1-5 and has become a standard preoperative diagnostic procedure at the Sydney Melanoma Unit, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia, for patients with cutaneous melanomas greater than 1 mm thick. When used in conjunction with blue dye injection immediately before surgery and a gamma probe during surgery, LS allows sentinel nodes in each draining node field to be located with great confidence.3,6,7 Unexpected lymphatic drainage patterns are not uncommon, and imaging protocols should therefore ensure that all sentinel nodes are located in each patient, even if the nodes are not located in standard node fields such as the axillary, groin, and cervical regions.

With an accumulated experience of more than 2000 lymphatic mapping studies in patients with melanoma, we observed drainage from the skin to a number of well-defined but not previously recognized lymph node fields, including the triangular intermuscular space,9 retroperitoneal and paraverterbral areas,9 and sentinel nodes over the right and left costal margins.10 We11 also regularly documented drainage to sentinel nodes in previously reported but sometimes overlooked sites such as the epitrochlear, popliteal, and occipital node fields. It is important to ensure that drainage to such sentinel nodes is detected during LS. This requires 5 to
MATERIALS AND METHODS

Using standard methods, previously described in detail elsewhere,12 LS was performed using technetiumTc 99m antimony trisulfide colloid in 2045 patients in 13 years. In the first 191 patients LS was performed to map lymphatic drainage patterns and thus identify the relevant draining node fields before elective lymph node dissection. These studies were performed in patients who had ambiguous drainage from primary melanoma sites on the trunk or head and neck. Since 1992, LS has been performed in 1854 patients to locate the sentinel lymph nodes for excision biopsy or for permanent skin marking of their surface location. Our imaging protocol when performing LS to identify sentinel nodes in patients with melanoma ensured that all of the territory between the melanoma site and the standard draining node fields was included in the field of view of the images obtained. This was achieved by using a large field of view digital gamma camera. The presence of interval nodes was recorded and correlated with the sites of the melanomas. In 21 patients who had an interval node excised as part of a sentinel node biopsy procedure, the presence or absence of micrometastases and the thickness of the primary melanoma was recorded in each case.

RESULTS

The primary melanomas in the patients studied with LS were on the posterior trunk in 755 patients, the anterior trunk in 150, the head and neck in 304, an upper limb in 385, and a lower limb in 451. Of 2045 patients, interval nodes were found in 148 (7.2%). The incidence of interval nodes in relation to the various primary melanoma sites is shown in the Table.

Of 21 patients who had interval nodes excised for histological examination, 3 (14%) had interval nodes that were positive for micrometastases. In all 3 of these patients, sentinel nodes also underwent biopsy in standard node fields, but no other sentinel nodes contained micrometastatic disease. In these 21 patients, the primary melanomas ranged in thickness from 0.7 to 12.5 mm (median, 2.6 mm). The 3 patients with metastatic disease in an interval node had melanomas that were 1.5-, 3.0-, and 4.2-mm thick.

In 127 patients who had interval nodes identified on LS, the nodes were not removed surgically. This decision was made in some patients because (1) the LS was performed before 1992 (before sentinel lymph node biopsy was described), (2) there were clinical factors that mitigated against surgical biopsy, (3) they were allocated to the observation arm of a sentinel lymph node biopsy trial, (4) they refused the surgery, or (5) the surgeon chose to ignore the finding of an interval node on LS.

The use of high-resolution LS to map lymphatic drainage pathways and locate the sentinel lymph nodes in large numbers of patients with melanoma has changed our understanding of the lymphatic drainage of the skin.13,14 It has become clear that precise patterns of lymph drainage are not predictable in individual patients on clinical grounds. Drainage to sentinel lymph nodes in unexpected places occurs frequently and will only be detected if high-resolution LS is a routine part of the sentinel node biopsy method. Lymph drainage from the skin to newly described node fields, such as the triangular intermuscular space, costal margin, and retroperitoneal and paravertebral areas, has been discovered in this way. Drainage to node fields that are sometimes overlooked, such as the epitrochlear and popliteal regions, is also demonstrated by LS. A recent study13 referred to nodes in the latter 2 node fields as “intercalated nodes” (another term that has been used for interval nodes), but we would regard these as standard node fields to be checked in all relevant patients. This same study referred to interval nodes in the upper thoracic wall, and we suspect that at least some of these might in fact have been nodes in the triangular intermuscular space. Drainage to all such sites will only be detected if imaging protocols acquire scans

<table>
<thead>
<tr>
<th>Melanoma Site</th>
<th>Patients, No.</th>
<th>Interval Nodes, No. (%)</th>
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<tbody>
<tr>
<td>Posterior trunk</td>
<td>755</td>
<td>96 (12.7)</td>
</tr>
<tr>
<td>Anterior trunk</td>
<td>150</td>
<td>11 (7.3)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>304</td>
<td>19 (6.2)</td>
</tr>
<tr>
<td>Upper limb</td>
<td>385</td>
<td>18 (4.7)</td>
</tr>
<tr>
<td>Lower limb</td>
<td>451</td>
<td>4 (0.9)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2045</strong></td>
<td><strong>148 (7.2)</strong></td>
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for 5 to 10 minutes over these areas. Lateral views of the upper thorax are also essential to detect drainage to nodes in the triangular intermuscular space. Failure to acquire images over these areas will mean that some sentinel nodes will be missed.

In addition to drainage to nodes in standard node fields, however, we have regularly seen drainage to true interval nodes that lie along the course of lymphatic vessels between the primary melanoma site on the skin and a recognized node field. There may be only a single interval node along the path of a lymphatic vessel, but they are sometimes multiple. The first interval node that the draining lymph reaches is by definition a sentinel node. A second interval node along the same vessel is a second-tier node, as is a node in a recognized node field that eventually receives lymph that has passed through a single interval node. In all but 2 of 21 patients who had surgical biopsy of their interval node, sentinel nodes in standard node fields were also present and underwent biopsy. These other sentinel nodes received tracer via a separate discrete lymphatic vessel and did not receive tracer that had passed through the interval node. Two patients (Figure 1 and Figure 2) had drainage exclusively to an interval node with no sentinel nodes in standard node fields. The patient illustrated in Figure 1 had a previous excision biopsy of a melanoma on the lateral aspect of the right elbow. The summed dynamic study showed 3 lymphatic vessels converging to an interval node on the medial aspect of the right upper arm at about the middle humeral level. A faint single lymph channel is visible passing onward from the interval node toward the right axilla. Right, The delayed scan performed 2 hours later shows activity in the interval node (vertical arrow) and fainter activity in the right axilla (curved arrow).

The sentinel node (interval node) did not contain metastases. Neither vessel bypassed the interval node. The only sentinel node was the first interval node reached by the lymphatic vessel, and on biopsy this node did not contain micrometastases. The next node along the channel is a second-tier node and not a sentinel node. Second-tier and above interval nodes, although less bright than the sentinel node in this patient, are readily identified, and it might be that interval nodes are more “porous” to the radiocolloid than nodes in recognized node fields. The typical finding on LS is that the tracer is retained in the sentinel node, with little if any tracer passing onward to second-tier nodes.

Interval nodes are also not uncommon on the upper back and posterior neck base, receiving drainage from melanoma sites high on the back.

In our patients, interval nodes were most commonly associated with primary melanomas on the posterior trunk (12.7% of patients), with about twice the incidence of interval nodes found elsewhere. From the skin of other parts of the body, the incidence of interval nodes was remarkably constant at about 5% to 8%, with the notable exception of the lower limb, where interval nodes were rare, occurring in only 1% of patients. This variation in the anatomical disposition of lymphatic vessels and nodes draining different parts of the skin is interesting, and we have seen similar variations in other features of the dermal lymphatics, such as the speed of lymph flow through the collecting vessels.

Of 21 interval nodes excised for histological examination, 3 (14%) harbored micrometastases. Although the numbers are small, this incidence of metastatic disease is of the same order of magnitude as is found in sentinel nodes generally in patients who have melanomas greater than 1.5-mm thick.11 These data support the proposition that any sentinel node, regardless of its location, can contain micrometastatic disease. This proposition is further supported by the recent finding18 that micrometastatic melanoma occurs in a significant percentage of sentinel nodes in the triangular intermuscular space subjected to biopsy. Although such nodes lie in an unusual location outside the traditional node fields known to drain the skin, when drainage occurs to them they seem to have the same chance of harboring metastases as lymph nodes.
in other node fields. The incidence of metastatic disease will presumably depend, as it does elsewhere, on the thickness of the primary melanoma.

On review of our data, 2 other patients were identified whose interval nodes were not subjected to biopsy initially but who developed recurrence at the site of the interval nodes shown on LS during follow-up, which varied from 3 months to 7 years. One patient had 2 interval nodes on the upper back that showed recurrent melanoma simultaneously 6 months after LS and the other had recurrence in an interval node in the right midaxillary line 17 months after LS. There were 2 other patients with primary melanoma sites on the head who developed local recurrence in the neck in the region where LS had shown interval and sentinel nodes in standard cervical node fields. The records of the histopathologic examination, however, do not make it clear whether the recurrence was in the interval node or one of the other sentinel nodes. Thus, there has already been clinical recurrence in 2 of 128 patients in whom the interval nodes did not undergo biopsy at the time of initial presentation and possible recurrence in 2 others. This is a surprisingly small number in view of the 14% incidence of micrometastases found in those interval nodes that underwent biopsy and suggests that clinical recurrence in interval nodes is uncommon or that recurrence is difficult to detect in these nodes. Nevertheless, as we found in individual patients, drainage to such nodes might be associated with recurrence at the site, and in some patients the only nodal micrometastatic disease present will be in an interval node. This was the case in our 3 patients who had an interval node positive for micrometastases on original excision biopsy. Other researchers also documented metastases in interval nodes. Interval nodes would thus seem worthy of surgical biopsy when found to be draining a cutaneous melanoma site.

In patients with cutaneous melanoma, the incidence of in-transit recurrence between primary tumor sites and local node fields has been reported to vary, depending on the thickness of the primary melanoma and the number of positive lymph nodes in the draining node field. It is interesting to speculate how often such in-transit metastases might actually have been metastases in previously undetected or unrecognized interval nodes. It may well be that many so-called in-transit metastases found before LS was routinely used were in fact metastases in interval nodes, which were actually sentinel nodes in those patients.

An apparent anomaly revealed by our data is the low incidence of interval nodes in the lower limbs. In our series, just 1% of patients with lower limb melanomas had interval nodes. This contrasts with the relatively common occurrence of in-transit metastases observed in the lower limbs, especially in the thighs. The inference is that most in-transit metastases that occur in the lower limbs are not occurring in interval nodes but by some other mechanism. A factor that might have affected this finding is that in patients with trunk melanomas, an in-continuity dissection was occasionally performed, and this therefore might have removed sites of potential in-transit metastasis in some of these patients. An in-continuity dissection was never performed in the lower limb unless the melanoma was high on the anterior thigh.

When describing the presence of interval nodes on LS it is important not to confuse them with lymphatic lakes, which are focal dilations of a lymphatic collecting vessel that can occur anywhere along its path. Lymphatic lakes are usually single but can be multiple; they do not contain any lymph node tissue and thus do not retain radiocolloid for long periods as lymph nodes do. On LS they are seen as bright focal areas on the course of a lymphatic vessel in the dynamic phase of the study, but they lose tracer rapidly, usually in 10 to 20 minutes. Occasionally lymphatic lakes take longer to fade, but they are usually not visible 2 hours after injection of the tracer. This is in contrast to interval nodes, which normally retain the radiocolloid for 24 hours or more.

Two final important points concerning the identification of interval nodes are the nature of the radiocolloid used for lymphatic mapping and the collimator used for gamma camera imaging. We used technetium Tc 99m antimony trisulfide colloid, which has a particle size in the 5- to 40-nm range. Colloids with this small particle size gain ready access to the initial lymphatics, thus lymphatic channels are clearly seen on early dynamic images and interval nodes are easily identified along the path of such channels. It also allows the separate discrete channels to be seen bypassing the interval nodes and passing to sentinel nodes in standard node fields. Interval nodes that are identified when using antimony sulfide colloid might not be seen at all when larger particle colloids are used.

High-resolution microcast collimators, which have minimal septal penetration at energies of 140 keV and thus have no significant “star” artifact, are also vital to obtain high-quality LS. Star artifact can completely obscure nodes close to the injection site. Folded metal collimators are subject to this artifact and are generally unsuitable for high-quality LS. If only folded metal collimators are available, it is preferable to use the medium-energy collimator supplied by the vendor. Although resolution will suffer, this does remove the problem of septal penetration producing a star artifact.

**CONCLUSIONS**

Preoperative LS using an appropriate small-particle radiocolloid and high-resolution collimators identifies interval nodes as sentinel nodes in a small but not insignificant percentage of patients with cutaneous melanoma. Drainage of lymph from the primary melanoma site to interval nodes that are sentinel nodes is associated with a 14% incidence of micrometastatic disease in these nodes. These might be the only sentinel nodes in the patient to contain micrometastases. Clinical recurrence might also occur in interval nodes that are sentinel nodes if they are not subjected to biopsy during initial surgical treatment. It is important that interval nodes not be overlooked if the sentinel node biopsy procedure is to be accurate in all patients.

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Serum Homocysteine Concentration as an Indicator of Survival in Patients With Acute Coronary Syndromes

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Background: Circulating homocysteine levels are predictive of survival in patients with stable coronary artery disease. The prognostic value of serum homocysteine levels, obtained in the acute phase in patients with myocardial infarction or unstable angina, is unknown.

Objective: To test the hypothesis that circulating homocysteine levels, obtained during the first 24 hours following hospital admission in patients with acute coronary syndromes, are predictive of long-term mortality.

Methods: To test this hypothesis we performed a prospective inception cohort study at a teaching hospital in Gothenburg, Sweden. A total of 579 patients (179 women and 400 men; median age, 67 years) were included (Q-wave myocardial infarction, non–Q-wave myocardial infarction, unstable angina in 206 patients, non–Q-wave myocardial infarction in 210 patients, unstable angina pectoris in 206 patients).

Main Outcome Measure: All-cause mortality.

Results: During a median follow-up of 628 days, 65 patients died. The serum homocysteine level (mean [SD]) was significantly lower in long-term survivors (n = 514) than in nonsurvivors (n = 65) (12.3 [7.0] vs 14.3 [5.9] µmol/L; P = .003). The relative risk (all-cause mortality) for patients with homocysteine levels in the upper quartile was 2.4 (95% confidence interval, 1.5-4.0) compared with that of patients in the 3 lower quartiles. After adjustment for relevant confounders, the relative risk estimate remained significant (relative risk = 1.69; 95% confidence interval, 1.02-2.80). In a stepwise model the homocysteine level provided prognostic information additional to that of patient age, diabetes mellitus, and diuretic usage prior to hospital admission (P = .03).

Conclusion: The serum homocysteine level on hospital admission is an independent predictor of long-term survival in patients with acute coronary syndromes. (2000;160:1834-1840)

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