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The Definition of a Sentinel Node

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Lymphatic mapping with sentinel node biopsy is one of the most interesting recent developments in surgical oncology. This approach allows patients with lymph node metastasis to be treated in an early phase without submitting other patients to unnecessary regional lymph node dissection.

The urologist Ramon Cabañas[1] was one of the first persons to use the name "sentinel lymph node." In 1977, he suggested that squamous cell carcinoma of the penis initially drains to a particular lymph node in the groin that is defined by its constant anatomic position. For penile cancer this assumption appears plausible, because penile cancer is always located in the exact same part of the body, quite unlike the situation in breast cancer and in melanoma.

In the late 1980s, Donald L. Morton, surgeon at the John Wayne Cancer Center in Santa Monica, and his pathologist Alistair J. Cochran (from UCLA) proposed the innovative concept of "lymphatic mapping with sentinel lymph node biopsy" for melanoma.[2] They suggested that the node to receive direct drainage from a melanoma could be any one node in a particular lymph node field, depending on the location of the primary lesion and with certain individual variability. By suggesting that other lymph nodes would become involved in a later phase, they revived William S. Halsted's (1852–1922) concept of sequential lymphatic dissemination.[3]

Lately, Morton's original definition of a sentinel node is becoming the source of confusion.[4–6] Morton stated: *a sentinel node is the initial lymph node upon which the primary tumor drains*.[2] In other words, the sentinel node (first-tier node, first-echelon node) is the lymph node on the direct drainage pathway from the primary tumor (Fig. 1). Some investigators have changed the definition and have come up with their own definitions.[7–10] This is understandable because specialists from different fields are involved and everybody is looking at this development from his or her own background and perspective. The purpose of this paper is to discuss these various definitions and to suggest a practical way to apply this information in the clinical situation.

Definitions Based on Lymph Node Location

It has been reported that some investigators define the sentinel node as the lymph node closest to the primary lesion.[11] This anatomical definition does not take into consideration the physiology of lymph drainage. The node closest to the primary tumor is the first one to be involved only when it receives direct drainage from the injection site (Fig. 2).

Definitions Based on Lymphoscintigraphy Interpretation

Early lymphoscintigraphy immediately after injection of the tracer visualizes the drainage pattern by delineating lymphatic channels and lymph nodes (dynamic or flow imaging). The radioactivity is cleared from the lymphatic channels and the late (static) images depict the lymph node(s) that contain the tracer. Most of the radioactivity stays behind at the injection site. Some investigators in the field of nuclear medicine define the sentinel node as the first lymph node that becomes visible on the lymphoscintigraphic images. Although the first node that is depicted is a sentinel node, this definition does not acknowledge the fact that more than a single sentinel

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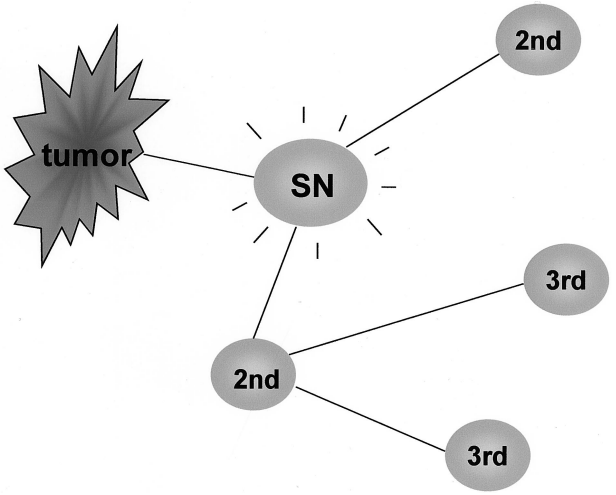

FIG. 1. The sentinel lymph node (SN) is the lymph node that receives direct drainage from the primary lesion. Second-tier and third-tier nodes receive drainage in a later phase.

node can be present. Dynamic scintigraphy and intraoperative blue dye mapping have made that clear. Sometimes there are two lymphatic channels originating in the region of the primary tumor and running to two different lymph nodes (Fig. 3). One of the two may be depicted on the scintigraphy images before the other. This does not imply that that other node is not a sentinel node. Both nodes are on a direct drainage pathway and tumor cells can travel through either duct and go to either node. There may even be more sentinel nodes than two. All these first-tier nodes should be harvested and examined by the pathologist. Therefore, the definition of the sentinel node being the first node to be visualized is too narrow: too few nodes are labeled sentinel node and metastases may be missed.

It is not unusual to see multiple lymph nodes light up on the lymphoscintigraphic images. Faced with that situation, some surgeons tend to regard only the "hottest"

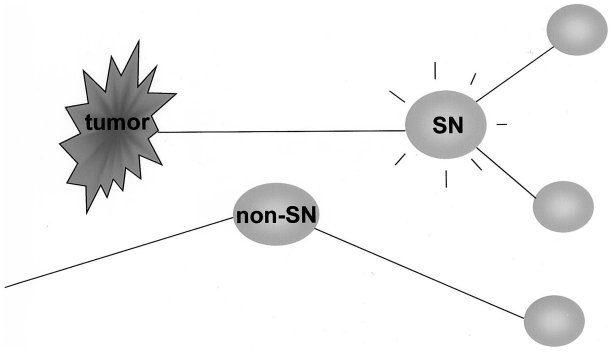

FIG. 2. Lymph from the primary tumor region does not necessarily travel to the nearest node.

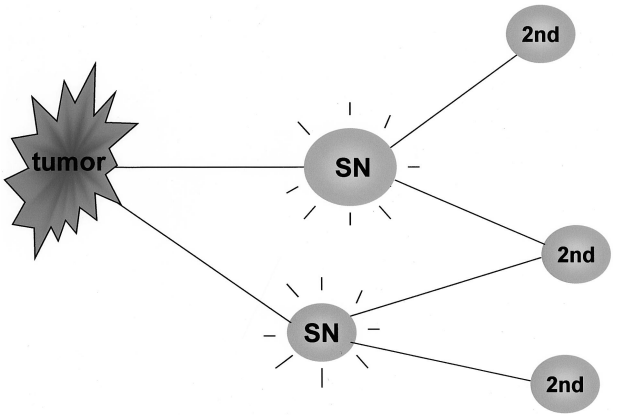

FIG. 3. Two lymphatic channels originating in the primary tumor running to two different sentinel lymph nodes (SN).

node as the sentinel node. That definition has several drawbacks. As indicated above, there can be more than one node to receive direct drainage from a tumor site. Furthermore, the amount of tracer that is accumulated by a node not only depends on its position in the drainage order but also on the number of lymphatic channels that enter the node and on parameters such as lymph flow rate. One of the reasons for a node to receive a sparse lymph supply is that the flow to that particular node is hampered by metastatic disease obstructing its ingress. This phenomenon is illustrated by a recent study of 176 patients: the positive node was the most radioactive node in only 60% of those in whom more than one sentinel node was identified.[12] The size of the node is another parameter that determines the amount of radioactivity that is accumulated.

Another relevant point is that the brightness of a node on the images not only depends on the amount of radionuclide in that node but also on its distance to the gamma camera. When two nodes containing an equal amount of a radionuclide are situated at a different depth, the node closest to the gamma camera will be depicted as the hottest (Fig. 4). Scatter and absorption explain this phenomenon: the brightness decreases with increasing distance. When two nodes not only have different depths but also different latitudes, one may be the hottest in the anterior view and the other one in the lateral view. So, there are a number of reasons not to use its brightness on the scintigram to decide whether or not a lymph node is a sentinel node.

Definitions Based on Use of the Probe

A gamma ray detection probe can be used to identify a sentinel node intraoperatively. Some surgeons assume that

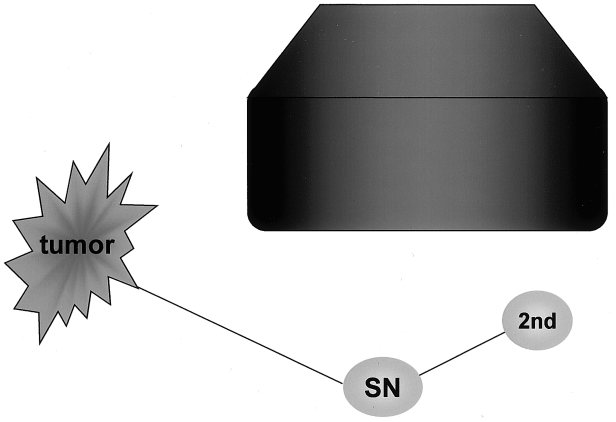

FIG. 4. Inverse square law of physics. A sentinel node that contains twice as much ^{99m}Tc as a second-tier node will appear less bright on the scintigraphic image when the distance between that node and the gamma camera is twice the distance between the second-tier node and the camera.

every radioactive node that can be identified with the gamma ray detection probe is a sentinel node and define a sentinel node as a radioactive node. This point of view does not acknowledge the fact that some of the tracer may pass through the first-tier lymph node and lodge in secondary nodes that are not directly at risk of harboring metastatic disease. So, this definition is too broad: too many nodes are removed. There are surgeons who, at times, remove up to fourteen radioactive nodes from a single lymphatic field and submit these as "sentinel" nodes! It is questionable whether an extensive exploration to recover that many lymph nodes is a more conservative procedure than a standard regional node dissection.

A more refined approach is to define a sentinel node as a node that contains a certain number of times as much radioactivity as the background: the *sentinel node-to-background ratio*. The amount of radioactivity that is accumulated in a lymph node depends on a number of factors, some of which are associated with the type of colloid particles that are used, such as their size, their surface characteristics, and stability. The size of the lymph node, macrophage avidity for the tracer, and the lymph flow rate clearly play a role as well. Lymph flow depends on factors such as physical exercise, medication, massaging of the injection site, and hydration of the patient. Because so many parameters are involved, it is not surprising that tracer uptake in a sentinel node is highly variable. In a study of 60 melanoma patients, uptake in the sentinel node ranged from 0.0013% to 6.8% of the injected tracer dosage.[13] In breast cancer, the 95% uptake range was shown to be 0.001% to 2.5% of the injected dose.[14]

The background count rate is also not the solid denominator it appears to be. Where is the probe placed to determine the background? Most surgeons obtain a background reading within the lymphatic field. This is notoriously variable and depends on the distance to the radioactive node, the distance to the injection site, and the angle at which the device is held. A background reading with a shield applied to the probe is considerably higher than a reading obtained with a collimator applied. A reading without shield or collimator is even higher.

Defining the sentinel node based on the *sentinel node-to-nonsentinel node ratio* also has its drawbacks. This approach implies that one has to find a nonsentinel node first and than check the other nodes with the probe to determine whether they exceed the designated count rate. Additional exploration is performed and this approach also requires a definition of the characteristics of a nonsentinel node. How many counts are acceptable for a node to be considered a nonsentinel node?

When we add to these considerations the notion that 15% to 30% of the lymph nodes on a direct drainage pathway from a primary breast cancer are not radioactive at all,[15,16] one cannot but conclude that the definition of a sentinel node had better not be based solely on factors measurable with the gamma ray detection probe.

Definitions Based on Use of the Vital Dye

Some surgeons remove every lymph node that is stained blue based on the definition of a sentinel node being a blue node. Again, this point of view does not acknowledge the fact that some of the tracer may pass through the first-tier lymph node and stain secondary nodes.

Occasionally, one is faced with a blue-stained lymphatic duct leading up to a lymph node that is not blue itself. Usually a few minutes of patience will be enough for the node to become at least partly stained. However, that may not happen. The ingress of lymph may be obstructed or the lymph flow may have stopped because the duct has suffered damage upstream. It seems reasonable to consider such an unstained node a sentinel node. Occasionally, a lymphatic vessel runs through the lymph node or over its surface without discharging its contents into that node.[17]

Concluding Remarks

The sentinel node is not a "blue node" or a "node with a certain amount of radioactivity." These characteristics are simply reflections of the technology that is applied to gain insight into the physiology of lymphatic drainage.[5]

Morton's original definition that a sentinel node is "the first lymph node that receives afferent lymphatic drainage from a primary tumor" best reflects the concept of the stepwise spread of cancer through the lymphatic system. However, this definition is based on the concept and it is not always of help when the nuclear medicine physician and the surgeon find themselves confronted with a clinical situation that is not as clearcut as the theory would suggest. Although excellent results have been described using blue dye or a probe alone, the most practical approach is probably to use all the available detection techniques in the repertoire. The scintigraphy images indicate the area to explore. The gamma ray detection probe can pinpoint the location of radioactive nodes. Careful dissection of the blue lymphatic channels lays out the drainage pattern and identifies the node(s) that receive drainage directly from the primary lesion. When the blue dye approach fails, it is best to err on the safe side and to remove the radioactive nodes that potentially could receive direct drainage from the primary lesion site.

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