Sentinel Lymph Node Localization

The most common radioguided surgery procedure is sentinel lymph node localization with radiolabeled colloids. Cabanas described the sentinel node methodology in patients with penile cancer in his groundbreaking 1977 publication (1). In that study, sentinel lymph node localization was accomplished with lymphangiography, using iodinated contrast material. Lymphangiography requires cannulation of lymphatic channels for the direct injection of an oily iodinated contrast agent. Lymph nodes are visualized on the radiographs as the contrast material passes from the injection site through the node. In contrast to the radiographic technique, when using radiocolloids no skin incision is required to study lymphatic drainage from a specific site. As a result, the radionuclide technique has replaced the x-ray technique.

The radionuclide method relies on the physiologic function of lymphatics in the skin and in most organs to transport the radiocolloid (2). The lymphatic vessels serve 2 major purposes in most tissues: first, the vessels transport extracellular fluid leaking from the capillary back to the central circulation; and second, the fenestrated lymph vessels pick up and transport small particulates (most likely intended for bacteria) to local lymph nodes, where the particles are phagocytized (3). The radionuclide technique exploits the latter property. Following intradermal, subcutaneous, or deep injections of radiolabeled colloids, the radiotracer localizes in lymph nodes draining the site of injection. This technique works well, although there are differences in the incidence of visualization of secondary and tertiary nodes, depending on the size of the colloidal particle.

In the mid-1950s, radionuclides (principally $^{198}$Au colloidal gold) were used to evaluate lymphatic drainage of the breast (4). This tracer had the major disadvantage of emitting beta particles, which caused a high radiation burden at the site of injection and set the stage for radioguided surgery to identify sentinel lymph nodes.

In addition to the radionuclide methodology, magnetic resonance agents and optical dyes have been advocated for identification of sentinel nodes (5). The magnetic resonance approach, however, requires imaging before and about 24 hours after administration of intravenous contrast material (6). The blue dye optical approach is widely employed in the operating room, but is limited by the transient localization of the dye in the nodes. The concept of histologic interrogation of a sentinel lymph node to identify the spread of tumor, coupled with the commercial availability of sensitive and handheld intraoperative gamma-detecting probes, has led to the wide acceptance of the radioguided technique by surgeons and oncologists (7).

Physiology and Anatomy

About 3 liters of lymph is produced daily. The average speed of lymphatic circulation varies in different regions of the body: for example, it is 1.5 cm/min in the head and neck regions, and 10.2 cm/min in the limbs. The speed of lymph circulation can be accelerated by ten- to thirtyfold when the muscles draining into the local lymphatic basin are working. Every 2 to 3 minutes, lymph vessels contract to propel lymph in the interstitial tissue to the lymph nodes (see Figure 1-1). The structure of the lymphatic capillaries and their connections with the surrounding tissues are represented in Figure 1-2. When lymph arrives at a lymph node, the fluid traverses a gauntlet consisting of exposed lymphocytes, plasma cells, and macrophages. Particulate materials in the lymph, such as radiocolloids, are phagocytosed by macrophages. Depending on the particle size and the particular path through the lymph node, some of the colloidal material (especially the smaller particles) proceeds through the efferent lymph vessel to the next node.
Sentinel Lymph Node Detection

Colloidal particles are introduced into the lymphatic circulation at or adjacent to the tumor site (8). Large colloids (between 200 to 1000 nm) are most useful to pinpoint the sentinel lymph node (see Figure 1-3, see Color Plate). Radiopharmaceuticals considered for detecting sentinel nodes should have the following characteristics:

- Labeled with technetium-99m
- A narrow range of particle size (to avoid high dispersion)
- Fast transport across the lymphatic chain and high retention in the node
- In vivo stability of the label
- Registered for human use

The characteristics of the colloidal agents—such as the particle size, pH, and the use of stabilizers—will influence the rate of tracer migration into the nodes, discomfort at the injection site, and the number of second- and third-tier lymph nodes visualized. Moreover, when the size is less than 4 to 5 nm, the particles are quickly cleared from the injection site through the blood capillaries. If the particles are less than 30 nm, they migrate rapidly and only a small proportion remains in the first lymph node, generating undesired visualization of additional nodes. On the other hand, particles between 30 to