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Mapping Sentinel Lymph Nodes among Patients Afflicted with Skin Melanoma

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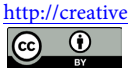

Abstract

The network of lymphatic vessels in the skin has been studied for centuries. In 1984, Sappey published an atlas of lymphatic vessels. The discovery of lymphoscintigraphy around 1950 renewed interest in verifying the pathways of lymphatic vessels in patients with skin melanoma. Lymphoscintigraphy quickly became an indispensable technique for mapping sentinel lymph nodes. Detecting sentinel lymph nodes is essential for conducting adequate diagnostics, appropriately staging patients, and administering necessary therapy. A sentinel lymph node is any lymph node that drains lymph from the tumor site. It may not even be the closest to the tumor site because lymphatic vessels can bypass that group of lymph nodes and drain into other lymph nodes. Lymphoscintigraphy is used in mapping sentinel lymph nodes in patients with skin melanoma. It involves intradermal injections of a radiocolloid in close proximity to the melanoma site or in the vicinity where an excisional biopsy has been performed. The location of all lymphatics is marked with a marker or tattooed with a dot on the skin above the node. Radiocolloids particles used for sentinel identification are in the size range of 5 - 50 nanometers. These particles easily enter lymphatic capillaries, and their entry is facilitated by exercise or massage of that body part. The lymphatic drainage of the skin varies from patient to patient, sometimes even when the tumor is in the same location in two different individuals. Therefore, careful diagnostics will enable the location of all true sentinel lymph nodes.

Subject Areas

Anatomy & Physiology, Oncology, Surgery & Surgical Specialties

Keywords

Sentinel Lymph Node, Lymphoscintigraphy, Mapping

1. Introduction

1.1. Network of Lymphatic Vessels of the Skin

The passage discusses the centuries-long study of the lymphatic vessels of the skin, particularly focusing on Sappey's work in 1984 when he published an atlas of lymphatic vessels. He identified lines on the human body, following which, according to his research, lymphatic vessels did not pass through. This simplified the prediction of the pathways of lymphatic vessels according to his scheme. The vertical line passed through the central line, both anteriorly and posteriorly, while the horizontal line passed at the level of the L2 spinal vertebra from the back and at the level of the navel from the front [1]. This practice was established for almost a century among physicians.

With the discovery and development of lymphoscintigraphy in the 1950s, there was a renewed interest in verifying the pathways of lymphatic vessels in patients with skin melanoma [2]. Scientists found that Sappey's rules did not always apply [3] [4], discovering so-called "ambiguous zones" near his defined boundaries where predicting the pathways of lymphatic vessels was not possible. Further research revealed that this was a space of about ten centimeters around previously established fictitious lines. Guided by this knowledge, doctors started using lymphoscintigraphy in patients with melanoma, especially when the lesion was in these "ambiguous zones," aiming to detect lymph nodes that drained lymph from this area before elective dissection of the entire group of lymph nodes. This was particularly useful for patients with melanoma near the midline, waist, or head and neck regions, where lymphoscintigraphy proved highly beneficial, as metastases in lymph nodes outside the marked region were very rare [5] [6] [7] [8] [9].

Morton and colleagues performed mapping of sentinel lymph nodes by injecting blue dye directly around the melanoma site [10], inspiring others to find simpler alternative solutions. Alex and others [11], as well as Krag and others [12], adopted Morton's technique, using a radiocolloid emitting gamma radiation to locate the sentinel lymph node with the help of a probe. Subsequently, lymphoscintigraphy quickly became a technique for mapping sentinel lymph nodes and is now an indispensable technique in preoperative preparation. In addition to preoperative injection of blue dye, lymphoscintigraphy is used intraoperatively where a probe is used to locate the sentinel lymph node emitting the highest gamma radiation. Currently, this combination of lymphoscintigraphy and blue dye injection is designated as the most precise method in detecting sentinel lymph nodes. This is necessary for conducting adequate diagnostics, ensuring proper staging of patients and administering necessary therapy [13]-[19].

1.2. Sentinel Lymph Node (SLN)

The term "sentinel" lymph node is any lymph node that drains lymph from the site of a tumor [20]. The sentinel lymph node (SLN) is not necessarily the first in the lymph drainage pathway, as lymph can be transported through lymphatic vessels in various directions that converge into different lymph nodes. Therefore, all these lymph nodes are considered sentinels. The SLN may not even be the closest to the tumor site, as lymphatic vessels may bypass that group of lymph nodes and drain into other lymph nodes. The best way to identify the SLN through lymphoscintigraphy is to visualize the lymphatic vessels draining lymph from the tumor region to the SLN during dynamic imaging. To successfully achieve this, it is necessary to have an appropriate number and size (small) of radioactive colloid particles in the lymph during early dynamic imaging [21].

1.3. Methods of Lymphoscintigraphy

Lymphoscintigraphy is used in mapping the sentinel lymph node (SLN) in patients with skin melanoma. It involves intradermal injections of 0.1 ml of radioactive colloid in each spot close proximity to the skin melanoma site or around the site of a previously excised skin melanoma. Typically, injections are performed at four locations, although the number may vary depending on the tumor's location. After the application of the radioactive colloid, dynamic imaging begins to trace the direction of lymphatic vessels' extension to the draining lymph nodes. During the imaging, it is essential to capture a image of 2 to 5 s/frame showing how the radioactive colloid drains through vessels into nodes, identifying the SLN and distinguishing them from secondary lymph nodes, which may also be visible.

After the dynamic imaging, the planar imaging is performed. It is usually performed at about 5 minutes intervals until the SLN is visualized. Images are taken from the front, back, and sides to better verify the lymph nodes. This part of imaging can take from 10 - 60 minutes if the melanoma is localized on the head or neck up to several hours if the tumor is on the other part of the body. The utilization of SPECT or SPECT/CT in SLN protocols has become significant due to reports indicating that protocols incorporating tomography are more effective than planar imaging in pinpointing SLNs. Particularly in cases of head and neck melanoma, where SLNs might be situated in close proximity to the primary tumor, integrating SPECT or SPECT/CT could assist in locating SLNs that may have been obscured during planar imaging due to their proximity to injection sites [22]. When we are sure we find the real SLNs, the locations of them are marked with an "X" marker or tattooed above the node. The depth of the SLN beneath the skin is measured by calculating the distance from the radioactive marker placed at the marked skin location. It is important to emphasize that the imaging and marking on the skin should be performed in the position that patient is going to have during surgery.

If possible, mapping of lymphatic vessels and nodes should be performed be-

fore radical excision of melanoma or expanding the protective margin around the excisional biopsy site to avoid disrupting the lymph drainage pathway and overlooking the true SLN [21]. The radioactive colloid must be such that it can enter the lumen of initial lymphatic vessels for adequate mapping. Initial lymphatic capillaries are terminal lymphatics without intraluminal valves, lacking a complete basal membrane and muscle layer [23] [24]. They are constructed by overlapping endothelial cells, with a space of about ten to twenty five nanometers between them. Elastic fibers on the outer side of endothelial cells are connected to collagen fibers in the interstitial matrix, allowing this space between endothelial cells to increase with tissue movement, such as exercise or massage, facilitating increased lymph flow. The entry of the radioactive colloid or blue dye into lymphatic vessels is also enhanced by exercising or massaging the tumor region. Conversely, external pressure, even minimal, reduces lymph entry into initial lymphatics. Lymph flow and entry into lymphatic capillaries are also reduced at low temperatures, therefore, the imaging room must be at least 21˚C. Lymphatic capillaries often form anastomoses between themselves, eventually grouping and forming lymphatic vessels with a three-layered wall and intraluminal valves [21].

The flow rate of lymph through lymphatic vessels varies depending on the region [25]. The fastest flow is observed in the area of the calf and feet, followed by the region of the forearm and hand. An average flow of three to four centimeters per minute is noted in the trunk, while the fastest lymph flow is observed in the head, neck and shoulder region. Lymphatic vessels possess an intrinsic pump mechanism that maintains lymph flow, but this mechanism can be influenced by increased hydrostatic pressure, increasing lymph flow (as occurs, for example, in the legs when standing) [26]. Lymph flow is also accelerated by heat and tissue inflammation. Although gravity negatively affects the flow rate, it does not influence the direction of drainage. Intraluminal valves inside lymphatic vessels enable unidirectional flow towards the lymph nodes [23].

1.4. Lymph Node

The retention of the radioactive colloid in lymph nodes involves complex processes rather than simple filtration. This process primarily entails opsonization, where the particles of the radioactive colloid are recognized as foreign to the organism [27]. This process can occur at the level of lymphatic vessels or at the level of lymph nodes, aiding in the subsequent phagocytosis of the particles. Reticulin fibers form a mesh-like structure in the sinuses of lymph nodes, slowing down the movement of particles and facilitating the phagocytosis process by macrophages and tissue histiocytes. These phagocytic cells are most abundant in the subcapsular sinuses, where the largest amount of radioactive colloid particles is retained [21].

Most of the radioactive colloid that reaches the lymph node will be retained by this process, regardless of the particle size. Therefore, when using small-particle

radioactive colloids such as ^{99m}Technetium-antimony sulfide, the sentinel lymph node (SLN) is the only lymph node labeled with the colloid in delayed imaging after two hours. A small amount of radioactive colloid may reach lymph nodes not labeled as sentinels, irrespective of the particle size, and it has been found to be directly related to the speed of lymph flow in afferent lymphatic vessels [28]. With an increase in lymph flow speed, the chance of radioactive colloid accumulation in non-sentinel lymph nodes also increases. Based on this, one could infer that a physiological process like phagocytosis, which retains radioactive colloid particles in lymph nodes, may be overcome if too many particles reach the lymph node in a short period [21].

1.5. Radioactive Colloids

The radio colloids used for identifying the sentinel lymph node are those whose particles have sizes ranging from five to fifty nanometers [29] [30]. These particles easily enter the lymphatic capillaries, and their entry is facilitated by exercises or massage of that part of the body, as previously explained. Considering the particle size, approximately five to eight percentage of the injected dose of radio colloid will migrate from the application site to the SLN [30]. Radio colloids with small particles that are used include filtered ^{99m}Technetium-sulfur, ^{99m}T-nanocolloid albumin and ^{99m}Technetium-antimony sulfide [21].

Radio colloids possessing large particles, with particles over two hundred nanometers, such as unfiltered ^{99m}Technetium-sulfur, face difficulties in migrating through the interstitial matrix and entering lymphatic capillaries, even with movement or massage of that part of the body. The majority of the applied dose remains at the injection site, despite massage or exercise, where less than one percentage of the radio colloid manages to reach the SLN [29]. Identification of the SLN in this case can be challenging. The problem with this approach is that one SLN may have lower radioactivity compared to others, and sometimes these "pale" lymph nodes may be the true SLNs [21].

The goal of the research is to emphasize the significance of lymphoscintigraphy as an essential component in mapping the sentinel lymph node and to observe modifications in the pathways of radioactive colloids spread through to lymph nodes.

1.6. Radiation Risks

For all the Sentinel Lymph Node (SLN) procedures discussed herein, the radiation exposure to patients remains minimal, significantly below the thresholds set by the International Commission on Radiological Protection. The annual radiation exposure for medical professionals regularly involved in SLN procedures, including nuclear medicine technologists, physicians, radiologists, surgeons, support staff, and pathologists, falls within acceptable limits—well below the specified occupational annual thresholds established by the International Commission on Radiological Protection. In the event that a pregnant woman requires

a Sentinel Lymph Node Biopsy (SLNB), the necessity of the procedure must be thoroughly assessed before its implementation. If deemed necessary, the procedure should proceed as planned, as both the radiation dosage to the patient and the fetus remain minimal and comply with regulatory guidelines [31].

2. Lymphatic Drainage Pathways from the Skin of Different Parts of the Body

2.1. The Posterior Part of the Trunk

The majority of lymph from this part of the body collects in the region of the sentinel lymph node in the axillary fossae, whether unilaterally, contralaterally, or bilaterally, while a smaller portion gathers in the groin. In this group of lymphatic drainage pathways, two unexpected routes of lymph drainage were discovered, and before the use of lymphoscintigraphy, it was unknown that these lymph nodes drain lymph from the skin of the posterior part of the body. More common than these two routes is the direction of lymph drainage into the triangular intermuscular space. The pathways from these lymph nodes continue to spread to lymph nodes in the axillary region, and they do not represent true SLNs. Without adequate lymphoscintigraphy and imaging, these lymph nodes in the axillary region may be mistaken for sentinels and excised, while the actual SLNs in the triangular intermuscular space remain untouched [21].

Another less expected route of lymph drainage from the skin of the posterior part of the trunk is the direct flow of lymph through the posterior body wall to paravertebral, paraaortic or retroperitoneal lymph nodes. The skin areas that typically drain lymph into these lymph nodes are the regions around the lumbar part of the back. Drainage of lymph to the SLN in these rare locations most commonly occurs in combination with lymph drainage to lymph nodes in more common areas such as the axilla and groin [21].

The most patients with melanoma in the region of the back have lymph drainage to much more common areas such as the axilla or groin, but a combination of both basins is often possible, especially when the tumor is located in the waist area. It has been observed that lymph from this location more frequently drains into axillary lymph nodes than into inguinal lymph nodes, especially if the tumor is located above the horizontal line of Sappey [21].

2.2. Front Part of the Trunk

Lymphatic drainage from the skin of the anterior part of the trunk generally flows into the expected lymph nodes. Even in the upper part of the anterior trunk, in the chest region, lymphatic vessels predominantly drain lymph to axillary lymph nodes rather than lymph nodes in the neck. Of course, there are always exceptions. A new lymph drainage route has been discovered that brings lymph from the periumbilical region skin to a lymph node located in the subcutaneous fat tissue above the rib line. The lymph pathway then continues medially, passing through the chest wall to the internal lymph nodes of the breast on

the same side as the lymph node in the region below the rib [30].

2.3. Head and Neck

The head and neck are challenging regions when it comes to mapping sentinel lymph nodes. Drainage to multiple SLNs simultaneously is common, and nodes are often small [16] [32]. SLNs are frequently located very close or sometimes even directly beneath the site of melanoma. Detecting these lymph nodes through lymphoscintigraphy is therefore very difficult, sometimes even impossible. Clinical predictions of lymph drainage pathways from the skin of the head and neck are unreliable, as it has been found that even in a third of patients, lymph drainage extends to nodes that are completely contrary to clinical predictions and expectations of where SLNs might be [33]. This occurs with melanomas on the skin of the face and the anterior part of the scalp. These regions drain lymph to retroauricular nodes, which are usually not excised during elective dissections. Drainage may also cross the midline, so sometimes, nodes on the contralateral side may be the only ones affected by metastasis. Additionally, lymph drainage from the lower half of the neck's skin may follow the direction of lymph nodes in the upper half of the neck or even to nodes in the occipital region. From the skin of the scalp, lymph drainage is toward the base of the neck or the supraclavicular region. Lymphatic vessels that bring lymph to these nodes completely bypass nodes in the upper and middle parts of the neck, retro- and pre-auricular (parotid) lymph nodes, as well as occipital nodes. These findings only confirm the concept that the SLN is not necessarily the lymph node closest to the site of the skin tumor [21].

2.4. Arm

Lymph drainage from the upper extremity is generally directed towards the axillary lymph nodes in almost all patients, although this may not always be the case. Drainage pathways of lymph to lymph nodes in the supraclavicular region, interpectoral region, neck or triangular intermuscular space have been discovered [20]. These patients had SLNs in both the axillary fossa and these regions mentioned above. Relying only on gamma probe guidance would remove only the axillary lymph nodes, leaving the nodes in these regions untouched [21] Therefore, adequate mapping with the help of lymphoscintigraphy is imperative.

2.5. Leg

Lymph from the skin of the lower extremities drains into lymph nodes on the same side of the groin, unless there has been prior surgery on those lymph nodes. In these situations, lymph drainage to contralateral lymph nodes may occur. Lymph drainage from the foot and leg to popliteal lymph nodes can also be observed. The range of skin areas on the leg that lead lymph to popliteal lymph nodes is expanded and not only from the plantar region, as previously thought [32].

3. Discussion

The routine practice of complete lymph node dissection as a preventive measure reveals metastases in 20% of patients. Consequently, about 80% of patients undergo surgical intervention without experiencing any clinical benefits. Adopting a strategy of observation is deemed unsatisfactory due to the anxiety it induces in patients regarding their uncertain prognosis. To address this issue, the Multicenter Selective Lymphadenectomy Trial I was initiated to determine if Sentinel Lymph Node Biopsy (SLNB) with intraoperative lymphatic mapping could detect the 20% of cases with hidden nodal metastasis [34]. This Phase 3 trial enrolled 2001 patients primarily with thin (<1 mm) or intermediate (1 - 4 mm) thickness cutaneous melanomas. Its primary objective was to evaluate the impact of SLNB on survival rates. Patients were randomly assigned to undergo SLNB followed by lymphadenectomy if nodal metastasis was confirmed on biopsy, or to be observed with lymphadenectomy reserved for nodal relapse. Although the study revealed no difference in melanoma-specific survival rates between the two groups, it demonstrated superior 10-year disease-free survival rates in the SLNB group compared to the observation group, especially among patients with intermediate-thickness melanomas and those with thick (>4 mm) melanomas [34]. While some experts remain skeptical about the conclusive effectiveness of SLNB based on this study, others interpret the results as indicative of SLNB becoming the standard of care [35]. Additionally, a 2010 meta-analysis involving non-randomized studies of 2633 patients suggested that SLNB was associated with improved survival rates and proposed that both SLNB and complete lymph node dissection might extend survival in one out of five treated patients after five years [36]. In 2005, the Multicenter Selective Lymphadenectomy Trial II commenced with the aim of enrolling 1925 subjects with sentinel node metastases. Subjects with a positive SLN are randomized to either undergo completion lymphadenectomy or receive observation with nodal ultrasound, with follow-up planned for ten years [37]. This trial seeks to address whether patients with a positive sentinel node require completion lymph node dissection, considering that 80% of such patients have no additional disease and may not necessitate complete lymph node dissection [38].

One of the primary advantages of nuclear medicine imaging has consistently been its superior functional resolution, exemplified by lymphoscintigraphy employing radiocolloids to identify the lymph node directly draining from a solid tumor site. This technique allows for the precise labeling and visualization of one or two sentinel nodes among the multitude of nodes present in the patient, offering clear identification on lymphoscintigraphy. However, this same method also highlights a drawback of nuclear medicine imaging: its limited anatomical resolution. Although the surface location of these sentinel nodes can be marked and the depth from the skin can be measured, planar nuclear medicine images do not provide detailed anatomical information [10]. Nuclear medicine imaging can be enhanced through the utilization of single photon emission computed

tomography (SPECT), which provides tomographic slices depicting the distribution of tracer within the patient's body. SPECT was pioneered in the late 1960s by Kuhl and Edwards in Philadelphia, preceding the development of computed tomography (CT) scans [39]. While SPECT images offered improved contrast of pathological lesions compared to planar scans, they still provided limited anatomical information. In lymphoscintigraphy, the anatomical data in SPECT scans is almost negligible. The limitations imposed by the low anatomical resolution of nuclear medicine images, whether planar or tomographic, are vividly exemplified in the case of 18F-flourodeoxyglucose (FDG) positron emission tomography (PET) scanning. This imaging modality was developed in the 1970s [40]. Minimal anatomical information was available, even in the three-dimensional (3D) tomographic PET displays. The scenario only underwent a transformation when hybrid imaging devices were introduced, enabling PET/CT scans to be conducted without necessitating patient moving.

PET/CT enabled accurate fusion of PET tomographic slices with corresponding CT anatomical slices, presenting PET functional data in color overlaid on the grayscale background of the CT image [41]. It is evident that SPECT/CT, the equivalent technology for single photon emitting radionuclides, is poised to have a similar impact on the clinical utility of these tracers. SPECT/CT, when incorporated into lymphoscintigraphy, serves as a prime example of merging the high functional resolution of nuclear medicine images (illustrating the radiolabeled sentinel node) with the high anatomical resolution of CT. This technology precisely identifies the sentinel node and provides detailed anatomical localization.

Numerous studies have demonstrated that in patients with melanoma, SPECT/CT offers several advantages over planar imaging. These advantages include increased sensitivity for sentinel node detection, identification of sentinel nodes in previously unrecognized nodal regions, improved detection of sentinel nodes located near the injection site, identification of deep pelvic sentinel nodes in patients with leg melanomas, and enhanced surgical localization by offering precise anatomical guidance [42] [43] [44]. An increasingly discussed issue in the diagnostic imaging literature pertains to the dosimetry of these procedures, particularly when employing hybrid devices. The crucial information provided by the CT image in SPECT/CT interpretation is the precise anatomical localization of the functional index lesion observed on the nuclear medicine SPECT image. A high radiation dose CT scan is unnecessary to obtain this localization, and I advocate for practitioners utilizing SPECT/CT hybrid imaging to employ the lowest feasible CT dose for each patient. A diagnostic CT scan with high radiation dose is simply unnecessary to derive the benefits of SPECT/CT, as it is the accurate identification of the "hot spot" that constitutes the essential data. This observation is equally applicable to PET/CT imaging [45]. SPECT/CT alone cannot substitute for the crucial information obtained during dynamic lymphoscintigraphy in melanoma patients. The precise identification of individual lymphatic collectors reaching the sentinel node (SN) on dynamic images remains the most accurate method for distinguishing between the SN and secondary-tier nodes

that subsequently receive the radiocolloid. Additionally, dynamic imaging provides other valuable data not captured by SPECT/CT, such as the dynamic arrival time of the tracer in the SN and the count of lymphatic collectors departing from the melanoma site, which serves as a guide for estimating the number of expected SNs and the corresponding lymph node fields they drain into. Furthermore, the relative intensity of the nodes is best depicted on planar scans.

While a secondary-tier node might appear adequately radiolabeled on SPECT/CT, it should not be labeled as a SN, and such a node should not be excised during a SN biopsy procedure. Doing so would undermine the crucial benefit of SN biopsy, which is to provide unparalleled nodal staging with minimal morbidity.

The integration of SPECT/CT into lymphoscintigraphy for locating the SN prior to surgical extraction represents the future and offers clear advantages for many patients with melanoma. However, it is imperative not to disregard dynamic lymphoscintigraphy, as doing so would risk losing the significant benefits in lymph node staging that have already been achieved using this technology [45].

4. Conclusion

Lymph drainage from the skin varies from patient to patient, sometimes even when the tumor is in the same location in two different individuals. The pathway of lymph vessels that collect and drain lymph is unpredictable, as are the locations of SLNs. Therefore, clinical predictions of SLN locations are unreliable and imprecise. Preoperative lymphoscintigraphy with small particle radio colloids allows visualization of all these lymph vessels draining lymph to SLNs. Careful diagnostics will enable the localization of all true SLNs, even when these lymph nodes are sometimes outside the usual lymph basin. This is crucial for accurate staging of patients with melanoma.

Conflicts of Interest

The authors declare no conflicts of interest.

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