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Lymphoscintigraphic Mapping Advancement for Melanoma and Breast Cancer

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Abstract

This paper combines the research and experience of nine recognized authors and publishers to analyze results and conclusions in the realm of lymphoscintigraphy. Many different radiopharmaceuticals have been used while determining the best option. Results of the studies and comparison to other similar procedures for lymph node mapping (LNM) is made. Sentinel lymph node (SLN) involvement and stage of the disease is characterized as variable and is explained, in detail, throughout this paper. There are varying opinions on the best route of administration, length of delay images and radiopharmaceutical to use. All of the discrepancies between protocols are supported with evidence such as positive results or false positive results. This paper will illustrate the different preferences of the procedure and the generally accepted protocols of the best way to locate the SLN. The series of images that are taken in lymphoscintigraphy must be sensitive enough to pick up on the SLN yet quickly clear from healthy lymph channels in order to distinguish the SLN from lymph channels. This creates a debate around which radiopharmaceutical is best for this study. Upon reading this paper, you will be able to form an opinion of the best protocols and radiopharmaceuticals based on the facts, all while seeing how lymphoscintigraphy is a crucial tool in taking steps to improve a patient's prognosis.

Keywords: sentinel lymph node, lymph node mapping, melanoma

Lymphoscintigraphic Mapping Advancing for Melanoma and Breast Cancer

Lymphoscintigraphy is a procedure that is used for tracking and treating how malignant cells travel through the lymph channels throughout the body. The lymph vessels that carry malignant cells follow patterns and trails, yet are still unique to each type of malignancy. Different radiopharmaceuticals and techniques impact the result of how adequately we are able to locate the sentinel lymph node(s).

Lymphoscintigraphy assesses lymphatic obstruction, lymph flow and malignancy of lymph nodes. The theory of lymph node mapping entails injection of a radioactive tracer, and imaging to follow the tracer route, where the tracer builds up and how far the tracer is able to travel. Lymphoscintigraphy relies on the sentinel lymph node and lymphatic channels in the individual patient. There are thousands of cellular and physical differences between human beings. This makes malignancies that travel in lymph channels one of the most dangerous. The exact placement of every sentinel lymph node (SLN) varies per individual. Regionally, lymph nodes are typically found in standard areas from patient to patient. This standardized, regional flow gives the familiar patterns among which SLNs are commonly found, however abnormal SLN discovery is not unusual.

Classification of Melanoma

More than 70,000 patients are diagnosed and over 9,000 will die from melanoma yearly (2009) *(1)*. Melanoma, a common cancer begins in the pigmented (dark) cells in the skin called melanocytes. Malignant melanoma is classified into Superficial Spreading Melanoma, Nodular Melanoma, Lentigo Maligna Melanoma, Acral Lentiginous Melanoma and Subungual

Melanoma *(1)*. In Table 1, subtypes of melanoma have been shown according to growth patterns, and potential of spread in specified individuals. All of these different types of melanoma follow different metastatic spreading patterns due to the individuality of the lymphatic system from patient to patient.

Melanoma Imaging Techniques

There are many variables that impact the quality of lymphoscintigraphic findings. Melanoma location and type, preparation of the radiopharmaceutical, injection technique and image views are incredibly crucial to the quality and constancy of lymphoscintigraphy findings. The radiopharmaceutical injection relies on the lymphatic system's ability to transport large molecules from the interstitial spaces back to the vascular system *(2).* The difference in molecule size presents different challenges such as lymphatic response. Responses that are too quick are unable to be captured in a nuclear image. Lymphatic responses that are much too slow make it difficult to find a SLN.

The ideal imaging agent for cutaneous melanoma lymphoscintigraphy would have a rapid clearance from the injection site into the lymphatic system, low radiation dose to the patient, good retention within the lymph nodes and correct particle size (depending on targeted findings).

There are two main types of tracers used, macromolecules and colloidal suspensions. Small particles (less than 100 nm) clear from the interstitial spaces while larger particles (greater than 500 nm) tend to remain at the injection site *(3).* Technetium-99m colloids are cleared more slowly from the injection site than macromolecules and do not show lymphatic vessels in great detail *(4)*. However, colloidal suspensions are trapped much more effectively in lymph nodes making them a more suitable radiopharmaceutical for lymph node mapping *(4)*. Because the

amount of radioactivity injected into the patient is microscopic (less than 1mCi), the radiation dose to the patient is often considered insignificant *(5)*. Regardless of the tracers used, injection technique is crucial to the procedure. Injections of material that are too large of an amount may cause a slow uptake of the radiopharmaceutical and also pose a threat of contamination on the patient's skin. Varying radiotracers produce variable uptake times. This is also impacted by the quality of the radiopharmaceutical injection.

The standardized and Society of Nuclear Medicine and Molecular Imaging (SNMMI) protocol for Melanoma Lymphoscintigraphy includes using Tc^{99m} Filtered Sulfur Colloid or Tc^{99m} Tilmanocept (Lymphoseek ®). The target dose is 15 MBq (0.5 mCi) administered intradermally or subcutaneously. The dose is divided equally among four syringes, these four injections are administered around the site of the lesion. Acquisition parameters depend on the region of interest (ROI). The camera is to be placed over the ROI acquiring a dynamic image for 30-60 minutes *(6)*. Static images are taken of the ROI and any visualized lymph nodes for 5-10 minutes. These static images should include axillary and inguinal views. Head and neck images should include anterior and posterior imaging. Additional views such as oblique or single photon emission computed tomography (SPECT) images may be acquired as needed. Sentinel lymph node location is to be marked on the skin. It is advised that imaging should not be acquired 15 hours post injection. *(6)*. Figure 1 shows an example of lymph node localization in the groin; melanoma is located on the thigh region.

Additional standard SNMMI options include using a transmission source, such as Cobalt 57 to delineate the body contour of the patient. Radioactive markers may also be used as reference points to provide more anatomical information. Anatomical reference points are subject to interpretation, however when a transmission source is included, the body contour is

illuminated. This provides a similar effect to a SPECT image, providing more than just counts per image, a body figure may be seen to help guide interpretations. Most of the time, patients are going to surgery following lymphoscintigraphy procedures. This transmission source body contour image allows the surgeon(s) to reference the image while in surgery for confirmation of the target lymph node.

Breast Lesion Classification

Malignant breast lesions are classified into five groups. B1 includes normal tissue that does not require further diagnostic testing. B2 is composed of benign lesions that have been biopsied and completed diagnostic testing. B3 involves lesions with potential for malignancy. Biopsy is necessary for B3 lesions to determine further action. B3 lesions can include papillary lesions, scar tissue and classic lobular neoplasia.

B4 lesions are confirmed malignancies. B5 malignant lesions are confirmed through biopsy and diagnostic imaging. These lesions are considered invasive carcinomas. Additional organs and systems are often involved when B5 lesions are confirmed.

Breast Imaging Techniques

Similar to melanoma lymphoscintigraphy imaging, there are many protocols in use that lead to differing results. The radiopharmaceuticals used are the same, Tc^{99m} Filtered Sulfur Colloid or Tc^{99m} Tilmanocept (Lymphoseek ®). Dose administered are also the same, ranging from 15 MBq (0.5 mCi) to 35 MBq (1.0 mCi). Injections should be subareolar or peritumoral, around the ROI. Standard SNMMI image acquisition includes a 30 minute dynamic image and

static images from 10-15 minutes per view. The tracer is to be administered 0.25-3 hours prior to surgery and no imaging should be performed 15 hours post injection *(7).*

Breast lesion lymphoscintigraphy findings are usually confined to the axillary area. Figure 2 illustrates lymphoscintigraphic findings of a SLN in the axilla. The depth of the lymph node is what makes this study more difficult to read. Although it is clear if SLNs are visualized in the axillary region, without body contour the reading physician is unable to pinpoint the lymph node for excision. Figure 3 shows an image including body contour by using a transmission source.

Sentinel Lymph Node Involvement

The sentinel node is the nodal site of potential micrometastasis. Sentinel lymph nodes are the main focus of lymphoscintigraphy because these nodes indicate where malignant cells will spread *first*. This defines the route of potential treatment and diagnosis of melanoma patients. The presence of regional lymph node involvement is the single most important prognostic factor. Assessing how far the tracer has traveled also predicts how far the malignancies have traveled. Sentinel nodes are the first draining node in the lymphatic chain. By identifying where the lymph fluid travels first throughout the body, mapping the route of malignancies is reached.

Sentinel lymph nodes are used to pinpoint where the tracer travels through a lymphatic chain. These chains are normal, free flowing channels throughout the entire body. When a SLN shows up on lymphoscintigraphy images, it does not mean that a malignancy has been found. The SLN is merely an indicator of where malignant cells are most likely to metastasize to first. By locating this node, surgeons are able to remove it and send the sample to be tested for presence of malignant tissue.

Downsides to Lymphoscintigraphy

Although lymphoscintigraphy clearly has many uses and benefits, such as tracking cancer before it has spread beyond borders, the lack of a standardized protocol hinders its full potential. Since lymphatics are unpredictable it is imperative that identical protocol is used when rescanning using lymphoscintigraphy techniques. Post operative scans are done at the three to six month mark. If the same protocol is followed, 85% of patients have consistency between the two scans identifying the same SLNs. Differing protocol may lead to false identification or a missed malignant node.

Abnormality definitions are also different among different institutions. This changes the staging, treatment plan and prognosis of each patient. If images are taken at zero minutes, 30 minutes, 120 minutes and 240 minutes at one institution and images are taken at zero minutes, 60 minutes and 240 minutes at another location (both protocols are widely used) comparison between patient images will be misleading. The radiopharmaceuticals used should also be standardized. If one institution scans with smaller particles and another scans with larger particles, the smaller particles will appear to travel much further than the large particles. Use of incorrect particle size can give a false negative if the large particle size remains at the injection site, allowing physicians to believe the malignant cells are not likely to spread.

Nissenkorn (2013) performed an evaluation comparison between lymphoscintigraphy and lymphangiography and computerized tomography (CT) scanning for whole body metastasis. A correct diagnosis was made in 61.5% of patients, while 23.1% had false positive results. False positive lymphoscintigraphy results were twice as common as the lymphangiography and CT scanning studies *(8)*. This demonstrates that even within the same health care facility, lymphoscintigraphy procedures can be inconsistent.

The standardization of lymphoscintigraphy protocols will lead to an advancement in the field that may surpass other modalities. If physicians are able to compare studies from around the world that are performed according to the same protocol, more patients will receive accurate treatment and preventative measures.

Practical Uses for Lymphoscintigraphy

Lymphoscintigraphy is also a preoperative tool. The lymphoscintigraphy images can identify and localize lymph node involvement before nodo venous shunt (NVS) procedures, sentinel node biopsies (SNB) and lymph node dissection. SNB is the most commonly used procedure in conjunction with lymphoscintigraphy. Early stage abnormalities may also be detected in unsuspicious areas when comparing the whole body images.

Lymphedema patients are also a large percent of lymphoscintigraphy studies. Assessment of lymphatic drainage pinpoints the area in which the channels are not draining as they should be. This malfunction causes a build up of fluid that is often painful. Lymphedema can be treated or managed to a functional state, once the ROI is defined *(7)*. Lymphedema is a very treatable condition. Lymphoscintigraphy provides the ability to pinpoint the origin of disease. This information can be used to repair these specific sites rather than treating the entire affected area.

Imaging technique is also crucial considering the views taken are to be compared pre- and post-therapy or surgery. Lymphoscintigraphy has improved the accuracy of melanoma staging using SPECT/computed tomography (CT) and positron emission tomography/CT (PET/CT) instrumentation. Many of the lymphatic drainage routes assessed by lymphoscintigraphy and SPECT/CT correspond with sites of lymph node metastases. Images taken differ based on timing, position and field of view. Flood sources are used to define the

body contour, this is able to depict more centrally located lymph nodes and delineate the nodes from lymphatic channels.

Throughout the world, there are thousands of institutions and hundreds of different protocols being used for lymphoscintigraphy. The consistency between images is unreliable for comparison when protocols are so diverse. Standardizing the protocol for such a widely used imaging modality would enable physicians to consult other cases similar when diagnosing and treating melanoma patients.

Lymphoscintigraphy and its Future Potential

The many protocols used in lymphoscintigraphy change the outcome of findings, not to mention the vast diversity between patients. Standardizing and focusing protocols among institutions that share images would give the patients a better, more accurate diagnosis. Lymphoscintigraphy is a widely available imaging test to evaluate lymphatic channels, melanoma staging and therapy prognosis. This procedure has the capacity to branch into use of other radiopharmaceuticals, using the same techniques to bring more diagnostic imaging into the medical world. For example, Tc^{99m} Filtered Sulfur Colloid is used to track the *potential* malignancies of melanoma and breast cancer, perhaps use of a different tracer yields the ability to track *defined* malignancies throughout the body. The field of lymphoscintigraphy is advancing everyday, yet protocol inconsistency may hinder the future of melanoma and breast cancer treatment.

No conflict of interest is associated with any of the referenced authors

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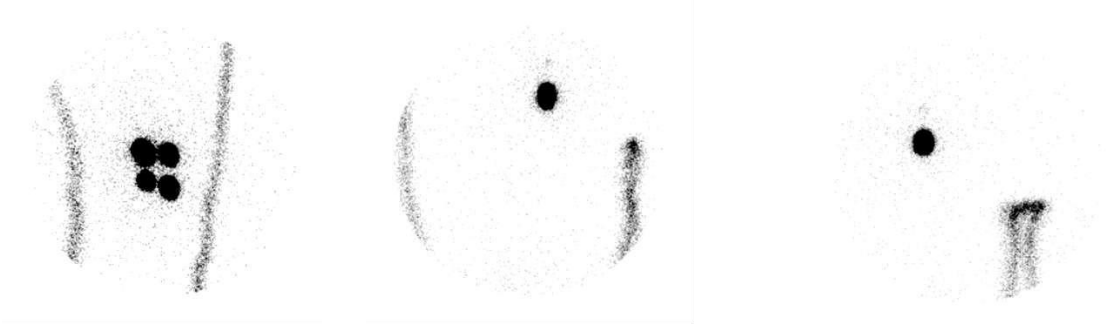
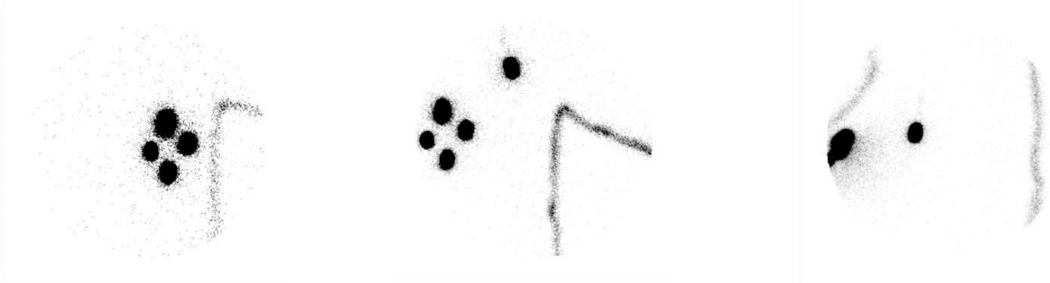
Figure 1 Leg Melanoma with visualized node in groin



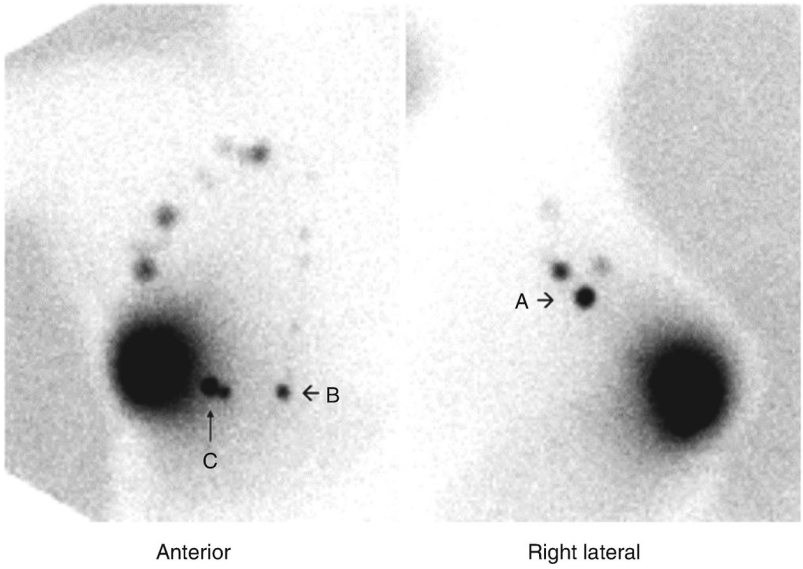
This image shows the localization of SLN in the groin area when an injection is performed at the thigh. The image provides an idea of the generalized regions in which lymph nodes are frequently found.

Figure 2 Breast lesion with visualized lymph node in axilla



This image is used in reference to figure 3. The comparison between images shows the benefits of using a transmission source when imaging SLNs.

Figure 3 Breast lesion lymphoscintigraphy with Co-57 transmission source (9)



This image is used to show how transmission sources can be an effective tool when trying to relate the internal node to an external site on the body. By giving the body an outline, the node is easier to mark for surgery. A shows the sentinel lymph node from a lateral view. B and C show other significant nodes, from an anterior view, in the region of interest. These nodes may also be removed for biopsy.

Table 1 Melanoma Subtypes

Subtype	Incidence	Location	Growth Pattern	Metastasis Potential	Gender Most Affected
Superficial Spreading	70%	Non weight bearing surfaces of the foot	Slow and radial	Low	Women
Nodular	15-30%	Non weight bearing surfaces of the foot	Rapid and vertical	High	Men
Lentigo Maligna	4-10%	Anterior lower leg in women, head and trunk in men	Slow and radial	Low	Women
Acral Lentiginous	2-8%	Palms, soles, nail beds	Radial at first then vertical	High	Women

This figure demonstrates the differences in melanoma types and how they impact the body. This figure also outlines who is most at risk for these specific subtypes of melanoma.