

Lymphoscintigraphy and clinic

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Abstract

Lymphoedema is a clinically unusual picture characterized by slowing down or block of the lymphatic circulation of limb or limbs affected, with progressively worsening evolution and appearance of recurrent acute lymphangitis complications, responsible for a further increase in volume and consistency of edema. The diagnosis or early identification of lymphoedema as well as its predisposition, can be revealed by lymphoscintigraphy. The sentinel lymph node individuation and surgical removal can be considered to be pro-procedure standard for many type of cancers, and preoperative lymphoscintigraphy has been recommended to confirm the successful uptake and direction of migration of radiotracer into sentinel nodes during lymphatic mapping.

Introduction

Lymphatic system refers to the number of vessels and lymphatic organs. The lymphatic vessels are made up of a complex system similar to the veins and arteries. Along the way they intersect the lymph nodes, lymphoid tissue formations, they get the sap from the vessels, these structures can be individual or grouped in large groups here and collect the sap that comes from the extended regions of the body [1].

Unlike the circulatory system, does not exist in lymphatic system an organ with central motor function; lymphatic vessels depart from the periphery and inside of the tissues and organs with a rate comparable to the venous system. Lymph is drained from lymph vessels, called true lymph and is derived from interstitial liquids, with the addition of the emolymph that filters from the capillaries of blood [2,3].

During the lymphatic circulation process, the body purifies the interstitial fluid by foreign substances, pathogens, metabolic products, debris of dead cells. The movement of lymph happens because of body movements that operate a mechanical compression on the lymphatic vessels and produce a progression of lymphatic fluid; the presence of valves prevents the lymph from coming back [4].

The presence of excess fluid in the tissues is defined as edema. Lymphatic edema corresponds to an increase in the size of a body area as a direct result of a decrease in lymphatic drainage, which occurs without increasing capillary filtration. It is generally considered secondary to the anatomical elimination of lymph vessels [5].

The lymphatic system is a network blind-end of vessels which plays an important role in mediating tissue homeostasis of the liquid, the intestinal absorption of lipids and the immune response. A deep understanding of the development of the lymphatic vessels as well as the molecular signals that govern their formation and morphogenesis could prove to be essential to our ability to treat lymphatic diseases.

The malfunction of the lymphatic vessels is associated with the pathogenesis of many diseases, including lymphoedema, fibrosis and inflammation. In malignant tumors, tumor-related lymph angiogenesis is an important mechanism by which metastatic cells spread to distant organs and lymph nodes.

Primary and secondary lymphoedema

About 10 million people have secondary lymphoedema for breast and pelvic cancer therapy, recurrent infections, vascular lesions, or surgery. Primary lymphoedema may be a non-hereditary or genetic condition; it can be one-sided or bilateral; it can occur at birth, puberty or adulthood [6]. The onset of edema is generally spontaneous without a history of trauma, surgery, or radiotherapy and more often occurs in patients before 30 or 35 years of age. The lower limbs are more frequently and severely affected by the upper extremities. The non-familial form is much more common than the family form. Worldwide, around 90 million people have lymphoedema, mainly due to parasitic infection. When chronic venous insufficiency is added as a cause, there may be up to 300 million cases. The two types of lymphoedema share the dysfunction of lymphatic endothelial cells that are involved in the absorption and transport of the lymph. The alteration of the lymphatic transport alters the clearance of the fluid from interstitium and macromolecules, thus affecting the osmotic and hydrostatic gradient maintained by the blood vessels [7].

The stagnation of interstitial blood for the presence of proteins, increases the colloid osmotic pressure, increasing the presence of edematous fluid, causing ischemia and local inflammatory reactions at the basis of chronic lymphatic insufficiency. The diagnosis of lymphoedema can be performed only with the physical examination: edema, orange peel skin, skin fibrosis, accentuation of skin folds at the metatarsophalangeal joints (sign Stemmers), thinning of the skin and subcutaneous tissue. In any case, the presence of lymphatic insufficiency can be confirmed by imaging techniques.

The lymphography by means of radiopaque contrast currently has a very limited role, whilst lymphoscintigraphy is regarded as high-

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resolution ultrasound examination together with echo-color Doppler, of the first level. The second level diagnostics involves the use of CT, MRI [8].

This diagnostic technique is not invasive and allows to evaluate the transport of the radiopharmaceutical along the lymphatic system, deep and superficial, view of the lymph node stations, to highlight the presence of a short circuit, stenosis, by-pass or flow conditioning ante grade or retrograde. Even if there are scan pictures indicative of some pathological conditions, the investigation in general does not allow diagnosis of etiological, even if it is able to diagnose a latent pathology lymphatic [9,10].

Based on the lymphoscintigraphic image pattern, it is often possible to determine whether the swelling of the limbs is due to lymphoedema and, if so, whether it is indicated the use of compression garments, or massage, or surgery. The effective use of lymphoscintigraphy to plan therapy requires an understanding of the pathophysiology of lymphoedema and the correct technical execution of the method [11].

Arm lymphoedema is a frequent complication of breast cancer therapy and axillary lymph node dissection, with an estimated frequency of 5%–30%. This incidence is based primarily on studies that use volume and circumference criteria in the first 2–5 y after surgery.

A combination of conservative surgery and careful patient selection for nodal radiotherapy may reduce the incidence of post mastectomy lymphoedema, particularly when these therapies are combined with sentinel node biopsy. Although axillary surgery staging, with or without breast conservation techniques, is considered relatively free from significant complications, a postoperative study of 200 patients suggested that lymphatic complications may still occur [12].

Lower-extremity lymphoedema resulting from treatment of pelvic cancer also occurs. The reported frequency of secondary leg lymphoedema ranges from 10% to 49%. Even “mild” lymphoedema of the leg may cause chronic leg discomfort and problems with walking, running, and fitting shoes [13].

Main applications of lymphoscintigraphy in lymphoedema

Already for many years, the guidelines of the International Society of Lymphology (I.S.L.) describes the lymphoscintigraphy as the “diagnostic gold standard” in the study of lymphoedema.

The tracer used in Nuclear Medicine for the execution of lymphoscintigraphy consists in colloidal nanoparticles made from a carrier platform, such as sulfur and stannous fluoride, with an imaging component, such as technetium. Sulfur colloid radioisotopes are the most commonly used carrier platform in the United States, with millions of doses prescribed since 1978. Albumin colloidal nanoparticles are an alternative platform and in Europe are used more than sulphur colloid nanoparticles. Their main advantages include a higher quantitative labelling yield and a smaller particle size (mean diameter of 30 nm, with most nanoparticles being below 80 nm). Their smaller size also allows for quicker migration through the lymphatic system but still adequate retention allowing their use in lymphoscintigraphy [14].

After the subcutaneous injection of the tracer in the interdigital spaces of the hands and/or of the foot, must be performed a revelation with a gamma camera of the distribution and of the times of appearance of lymph nodes. According with the Italian Association of Nuclear Medicine (AIMN) guidelines, the first after 20’/30’, than must

be stimulated the muscular pumps of the limbs for 15 minutes and subsequently perform another revelation with a gamma camera after 120’ from the injection. Acquisition is preferably done in whole body mode for legs and in planar mode for arms.

The examination, quite simple execution, provides morphological and functional indications in the lymphatic circulation, but it seems necessary to have a good understanding of the clinical information by nuclear physicians and lymphangiologists.

Criteria for the diagnosis of lymphatic dysfunction include delayed, asymmetric or absent visualization of regional lymph nodes, asymmetric visualization of lymphatic channels, collateral lymphatic channels, interrupted vascular structures, and visualization of the lymph nodes of the deep lymphatic system. The appearance of tracer outside the main lymph routes, particularly in the skin, so called “dermal back flow”, indicates lymph reflux and suggests proximal obstruction. Poor transit of isotope from the injection site suggests hypoplasia of the peripheral lymphatic system [15]. In a cohort of 465 consecutive patients, we observed [16] that the dermal back flow generally is proportioned to the clinical stage of lymphoedema; it’s partially regressing after treatment and can be present also with healthy lymphatic station (for example in the post phlebotic syndrome or in iatrogenic lesions of lymphatic trunks).

Although reproducibility studies are missing, a lymphoscintigraphic evaluation of the upper limb is often used in routine practice to diagnose lymphoedema and in clinical research, for example, to investigate the effect of a physical treatment. Some authors [17] conclude that a lymphoscintigraphy of the upper limb is a reproducible imaging tool to assess the lymph transport quantitatively—for percentage extraction of radiotracer from the hands and percentage uptake of radiotracer in the axilla in the late phase and the increase of uptake in the axilla from the early to the late phase—and qualitatively. In the field of reproducibility a scoring system for qualitative evaluation of lymphoscintigraphic imaging of lower extremities has been proposed, but some author are favourable [18] and others not favourable [19].

Lymphoscintigraphy is also used to define the clinical characteristics, investigations, management and outcomes of lymphoedema in paediatric patients [20].

In a series of patients treated with vascularised lymph node transfer (VLNT) some authors concluded that at present, vascularised lymph node transfers have their role in moderate to severe lymphoedema valuated by means of lymphoscintigraphy [21].

Regarding the other known surgical procedure for lymphoedema treatment, microsurgical LVA, Campisi *et al.* [22] conclude that have a place in the treatment of peripheral lymphoedema, and should be the therapy of choice in patients who are not sufficiently responsive to nonsurgical treatment. Microsurgical derivative and reconstructive operations can restore lymphatic drainage, both in the short and long term, and the best results are obtained when these surgical procedures are combined with physical rehabilitative methods, and lymphoscintigraphy is useful in verifying the patency of microanastomoses long term after operation by direct and indirect findings: reduction of dermal backflow together with the appearance of preferential lymphatic pathways not visible before microsurgery; disappearance of the tracer at the site of LVA due to direct tracer passage into the blood stream. This is particularly true in microsurgical techniques based on histological and immuno-histochemical findings [23]. Also, it is demonstrated that LVA can release the pain in the

affected limbs of lymphoedema [24].

Another surgical procedure of lymphoedema with previous lymphoscintigraphic diagnosing and subsequent lymphoscintigraphic follow up, consists in autologous lymph vessel transplantation [25]. The authors concluded that lymphoscintigraphy is helpful not only in planning microsurgical treatment but also in monitoring the postoperative outcome that they performed for 8 years.

In our casuistry [26] we have pointed out 5.9% of iatrogenic secondary lymphoedema, understanding with this term, lymphoedema provoked by medical or surgical or physiotherapeutic procedures responsible of damage to the lymphatic trunks. In these cases, we underline the importance of lymphoscintigraphy. In particular among patients who undergone an aorto-coronary by-pass [27], the appearance of an oedema in a partial saphenic phlebectomy, only in some cases it appeared an early or late but persistent post-surgical lymphoedema, while in about the 71% surgery had not changed the normal lymphatic flow in the operated limb, so suggesting that it could be possible to avoid iatrogenic lymphoedema in predisposed subjects, selected on lymphoscintigraphy previous to surgery.

Particular cases of lymphoscintigraphic application

Chyluria is a medical condition with presence of chyle in urine. The disease is most prevalent in South East Asian countries mostly caused by parasitic infections. Sometimes visualization via lymphoscintigraphy is unrevealing [28] and in other cases is considered very useful [29].

In a case of thoracic duct injury, lymphoscintigraphy, not in planar modality, but using a SPECT-CT hybrid apparatus, because planar lymphoscintigraphy lacks accurate anatomical depiction which SPECT-CT could offer, overcomes the limitation of either imaging alone. It has been reported to be valuable in documenting and depicting sites of injury, thus confirming the bilateral leakage sites being pivotal in guiding the surgeon to take a different approach and achieve a permanent solution to the persistent chloroethoxy [30].

In the 1990s, several studies used ^{99m}Tc -colloid lymphoscintigraphy to demonstrate lymphatic dysfunction in patients with Rheumatoid Arthritis or psoriatic arthritis who developed lymphoedema in their arthritic extremities [31]. In the majority of these case reports, lymphoedema lessened when arthritis improved after therapy; this was associated with normalization of colloid uptake assessed by lymphoscintigraphy [32].

Advances of the application of autologous hematopoietic stem cells in ischemic disorders of lower limbs have increased the attention of researchers in this field. Peña *et al.* [33] in a cohort of 65 patients submitted to stem cell implantation observed that the isotopic lymphography can evaluate the therapeutic response and its intensity, therefore lymphoscintigraphy is a useful technique for the evaluation and monitoring of autologous stem cell transplantation in patients with chronic lymphoedema.

In a 38-year-old man with a high fever and acute abdominal pain, abdominal lymphadenopathy and with HIV infection was diagnosed, and obstruction or destruction of the thoracic duct by disseminated non-tuberculous mycobacterial infection was considered as a possible cause of the chylothorax. Lymphoscintigraphy confirmed lymphatic obstruction and thoracic duct leakage [34].

Main applications of lymphoscintigraphy in the sentinel lymph node

The term sentinel lymph node was used for the first time the urologist Ramon Cabanas in 1977 for the hypothesis that carcinomas epidermoid carcinoma of the penis drains initially in a specific lymph node in the inguinal region, defined by a precise anatomical location [35]. Morton and the pathologist Cochran in 1992 developed the innovative concept of "mapping the lymph through the biopsy of the sentinel lymph node" in melanoma [36]. They argued that the lymphatic drainage of a melanoma is addressed directly to one specific lymph node, in a specific station, the employee from the seat of the primary lesion, although with some individual variability.

This lymph node was called the sentinel, as a detector of the state of disease of the lymph nodes drainage, in homage to the concept of dissemination of lymphatic sequential. The fundamental innovation of the use of a radionuclide as a tracer is due to Alex and Krag 1993, which described the intradermal injection of sulfur-colloid labeled with ^{99m}Tc , followed by the lymphoscintigraphic study and surgical radiolocalization [37]. The concept of the sentinel lymph node since then has been studied extensively, validated by numerous studies and is today universally considered to be pro-procedure standard for melanoma and for cancers of the breast [38-41].

The dissection of axillary lymph nodes, in addition to the excision of the primary tumour, has been for a long time the standard surgical procedure for patients with breast cancer; furthermore the axillary dissection can provide an excellent loco-regional control of the disease. However, it is necessary to emphasize that, in prospective randomized trials has never been demonstrated a significant increase in survival for patients treated with axillary dissection, compared to patients who did not perform this procedure. In addition, the draining axillary can cause unpleasant complications such as pain, paresthesia, and lymphedema [42].

Preoperative lymphoscintigraphy has been recommended to confirm the successful uptake and direction of migration of radiotracer into sentinel nodes during lymphatic mapping for breast cancer [43]. In addition, preoperative lymphatic mapping may provide a visually useful aid to the relative location of sentinel nodes within a nodal basin [44,45].

Furthermore, the method does not provide radioactive dose to operators in the surgical room [46].

Sarri *et al.* [47] evaluated early variations in lymphatic circulation of the arm pre- and post-SLNB and conservative breast surgery by means of lymphoscintigraphic study. They concluded that, although further studies are needed to confirm their findings, monitored by lymphoscintigraphy, upper limb lymphatic flow gradually decreased after an SLNB.

The staging of lymph node status in cutaneous melanoma is of great importance in the management of patients with early stage melanoma (clinical stages I and II). If the sentinel lymph node is negative for metastases, the likelihood that the remaining loco-regional lymph nodes are affected by metastasis is <1% [48].

The lymphoscintigraphy is necessary to map the area of the skin, the seat of melanoma. Lymphatic mapping using radio colloid reveals ways unexpected of lymphatic drainage, it finds all the stations lymph node at a greater risk of metastasis and for each of them, locates the sentinel lymph node; it also allows the identification and biopsy of the lymph nodes in-transit (the lymph nodes under the skin spots between the seat skin of the melanoma and the station lymph node

main) [49,50]. With the new generation of large -field of view gamma cameras, SPECT/TC has been incorporated in the SLN procedure. The functional information from SPECT can be combined with the morphological information from CT applying both techniques in one session [51]. The resulting SPECT/TC fused images depict sentinel nodes in their precise anatomical setting, thus providing a helpful roadmap for surgeons.

Sentinel node technology has also been used in both gynecologic and urologic applications. For gynecology, successful application of sentinel node techniques in endometrial [52] cervical [53] and vulvar cancers [54] have been described. Urologic applications have included prostate [55] and bladder [56] cancers.

A certain utility has also been found in sentinel lymph node lymphoscintigraphic research and radio guided surgery in oral cavity carcinoma [57,58].

Sentinel node (SN) mapping for early gastric cancer have shown acceptable SN detection rates and accuracy of determination of lymph node status [59].

Mediastinal lymph node dissection is an integral part of non-small cell lung cancer (NSCLC) surgical treatment. Sentinel lymph node (SLN) mapping and biopsy has been proposed as an alternative to mediastinal lymph node dissection in NSCLC since 1999 [60]. The prerequisite of preoperative lymphoscintigraphy imaging is preoperative CT- or bronchoscopy- guided injection of the radiotracer. For intraoperative SLN detection, an acoustic gamma detection probe is used to guide the surgeons to the location of SLN. SLN mapping and biopsy needs careful selection of patients (only cN0 patients without history of chemo-therapy) and proper administration route of the radiotracer (peritumoral injection is preferred over intratumoral injection) [61].

References

- Olszewski WL (1991) Lymphology and the lymphatic system. In: Olszewski WL, ed. *Lymph Stasis: Pathophysiology, diagnosis and treatment*. Boca Raton, FL: CRC Press; 4-12.
- Sjöberg T, Steen S (1991) Contractile properties of lymphatics from the human lower leg. *Lymphology* 24: 16-21. [Crossref]
- Ohhashi T, Kawai Y, Azuma T (1978) The response of lymphatic smooth muscles to vasoactive substances. *Pflugers Arch* 375: 183-188. [Crossref]
- Lubach D, Lüdemann W, Berens von Rautenfeld D (1996) Recent findings on the angioarchitecture of the lymph vessel system of human skin. *Br J Dermatol* 135: 733-737. [Crossref]
- Aukland K, Reed RK (1993) Interstitial-lymphatic mechanisms in the control of extracellular fluid volume. *Physiol Rev* 73: 1-78. [Crossref]
- Campisi C (1999) Global incidence of tropical and non-tropical lymphoedemas. *Int Angiol* 18: 3-5. [Crossref]
- Szuba A, Rockson SG (1998) Lymphedema: classification, diagnosis and therapy. *Vasc Med* 3: 145-156. [Crossref]
- Bettmann MA, Levin DC, Gomes AS (2000) Sudden onset of cold, painful leg. American college of radiology appropriateness criteria. *Radiology* 215:101-105. [Crossref]
- Campisi C (1991) A rational approach to the management of lymphedema. *Lymphology* 24: 48-53. [Crossref]
- Keeley V (2006) The use of lymphoscintigraphy in the management chronic oedema. *J Lymphoedema* 1:42-57.
- Weissleder H, Weissleder R (1988) Lymphedema: evaluation of qualitative and quantitative lymphoscintigraphy in 238 patients. *Radiology* 167: 729-735. [Crossref]
- Roses DF, Brooks AD, Harris MN, Shapiro RL, Mitnick J (1999) Complications of level I and II axillary dissection in the treatment of carcinoma of the breast. *Ann Surg* 230: 194-201. [Crossref]
- Szuba A, Shin WS, Strauss HW, Rockson S (2003) The third circulation: radionuclide lymphoscintigraphy in the evaluation of lymphedema. *J Nucl Med* 44: 43-57. [Crossref]
- Thakor AS, Jokerst JV, Ghanouni P, Campbell JL, Mitra E, Gambhir SS (2016) Clinically approved nanoparticle imaging agents. *J Nucl Med* 57: 1833-1837. [Crossref]
- Keo HH, Gretener SB, Staub D (2017) Clinical and diagnostic aspects of lymphedema. *Vasa*. [Crossref]
- Mango L, Michelini S, Failla A, Moneta G (2005) Lymphoscintigraphy and clinical evidence. *The European Journal of Lymphology* 15:27.
- Devoogdt N, Van den Wyngaert T, Bourgeois P, Lambrechts M, Van Kampen M, et al. (2014) Reproducibility of lymphoscintigraphic evaluation of the upper limb. *Lymphat Res Biol* 12: 175-184. [Crossref]
- Ebrahim M, Savitcheva I, Axelsson R (2017) Reliability of a scoring system used for qualitative evaluation of lymphoscintigraphic imaging of lower extremities. *J Nucl Med Technol* 116. [Crossref]
- Mango L, Ventroni G, Semprebene A (2016) Linfoscintigrafia e sue integrazioni. Importanza del Transport Index Proc. 2nd Nat Cong. International Lymphoedema Framework (ITALF) Ancona (Italy) 18-19 novembre.
- Watt H, Singh-Grewal D, Wargon O, et al. (2017) Paediatric lymphoedema: A retrospective chart review of 86 cases. *J Paediatr Child Health* 53: 38-42. [Crossref]
- Loh CY, Wu JC, Nguyen A, Dayan J, Smith M, et al. (2017) The 5th world symposium for lymphedema surgery—Recent updates in lymphedema surgery and setting up of a global knowledge exchange platform. *J Surg Oncol* 115: 6-12. [Crossref]
- Campisi C, Bellini C, Campisi C, Accogli S, Bonioli E, et al. (2010) Microsurgery for lymphedema: clinical research and long-term results. *Microsurgery* 30: 256-260. [Crossref]
- Boccardo F, Fulcheri E, Villa G, Molinari L, Campisi C, et al. (2013) Lymphatic microsurgery to treat lymphedema: techniques and indications for better results. *Annals of plastic surgery* 71: 191-195. [Crossref]
- Mihara M, Hara H, Zhou HP, Tange S, Kikuchi K (2017) Lymphaticovenous Anastomosis Releases the Lower Extremity Lymphedema-associated Pain. *Plast Reconstr Surg Glob Open* 5: e1205. [Crossref]
- Weiss M, Baumeister RG, Hahn K (2003) Dynamic lymph flow imaging in patients with oedema of the lower limb for evaluation of the functional outcome after autologous lymph vessel transplantation: an 8-year follow-up study. *Eur J Nucl Med* 30: 202. [Crossref]
- Michelini S, Failla A, Moneta G, Mango L, Iannacoli M (2001) Iatrogenic secondary lymphedema: a reality to be avoided. *The European journal of Lymphology* 9: 99.
- Michelini S, Failla A, Moneta G, Mango L (2005) Iatrogenic post-saphenectomy lymphedemas following aorto-coronary bypass. *The European journal of Lymphology* 15: 18.
- Mendu DR, Sternlicht H, Ramanathan LV, Pessin MS, Fleisher M, et al. (2017) Two cases of spontaneous remission of non-parasitic chyluria. *Clin Biochem* S0009-9120: 30385-5. [Crossref]
- Yuan Z, Luo Q, Chen L, Luo Q, Zhu R (2010) The role of radionuclide lymphoscintigraphy in chyluria. *Hell J Nucl Med* 13: 238-240. [Crossref]
- AbAziz A, Yusop SM, Tahir MFM, Lim YC, Gallowitsch, HJ (2016) Lymphoscintigraphy SPECT/CT: Instrumental navigator in repair of thoracic duct injury. *Nucl Med Mol Imaging* 50: 173-174. [Crossref]
- Böhm M, Riemann B, Luger TA, Bonsmann G (2000) Bilateral upper limb lymphoedema associated with psoriatic arthritis: a case report and review of the literature. *Br J Dermatol* 143: 1297-1301. [Crossref]
- Rahimi H, Bell R, Bouta EM, Wood RW, Lianping Xing, et al. (2016) Lymphatic imaging to assess rheumatoid flare: mechanistic insights and biomarker potential. *Arthritis Research & Therapy* 18:194.
- Peña Y, Batista JF, Perera A, Torres LA, Sánchez EL, et al. (2016) Lymphoscintigraphy and autologous stem cell implantation. Proceedings of V International Seminar and V National Workshop 'Use and development of products isotopic health industry' 20th anniversary CENTIS, (pp. 1CD-ROM). Cuba: Centro de Isotopos CENTIS, Mayabeque, Cuba.
- Tanaka T, Saito N, Takaki M, Furumoto A, Morimoto K, et al. (2016) Refractory chylothorax in HIV/AIDS-related disseminated mycobacterial infection. *Thorax* 1-2.
- Cabanas RM (1977) An approach for the treatment of penile carcinoma. *Cancer* 39: 456-466. [Crossref]

36. Morton DL, Wen DR, Wong JH, Economou JS, Cagle LA, et al. (1992) Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 127: 392-399.[Crossref]
37. Krag DN, Weaver DL, Alex JC, Fairbank JT (1993) Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. *Surg Oncol* 2: 335-340.[Crossref]
38. Somasundaram SK, Chicken DW, Keshtgar MR (2007) Detection of the sentinel lymph node in breast cancer. *Br Med Bull* 84: 117-131.[Crossref]
39. Veronesi U, Paganelli G, Galimberti V, Viale G, Zurrada S, et al. (1997) Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. *Lancet* 349: 1864-1867. [Crossref]
40. Gucciardo G, Schiavo R, Grillo LR, Mencacci R, Mango L, et al. (2000) The success rate of identification of the sentinel lymph node in breast cancer: our training series. *Tumori* 86: 312-313.[Crossref]
41. Veronesi U, Viale G, Paganelli G, Zurrada S, Luini A, et al. (2010) Sentinel lymph node biopsy in breast cancer: ten-year results of a randomized controlled study. *Ann Surg* 251: 595-600.[Crossref]
42. Hill ADK, Frsci MCH, Tran KN, Akhurst T, Yeung H, et al (1999) Lessons learned from 500 cases of lymphatic mapping for breast cancer. *Ann Surg* 229: 528-535. [Crossref]
43. Mariani G, Erba P, Villa G, Gipponi M, Manca G, et al.(2004) Lymphoscintigraphic and intraoperative detection of the sentinel lymph node in breast cancer patients: The nuclear medicine perspective. *J Surg Oncol* 85:112-122. [Crossref]
44. Mango L, Ventroni G (2013) Sentinel node mapping in breast cancer: drainage to multiple axillary nodes after intradermal injection (Planar Imaging). In: G. Mariani et al. eds, Atlas of Lymphoscintigraphy and Sentinel node Mapping. Springer pp.139.
45. Kenneth AK, Rosenberg RJ (2000) Preoperative lymphoscintigraphy during lymphatic mapping for breast cancer: improved sentinel node imaging using subareolar injection of technetium 99m sulfur colloid.*J of the American College of Surgeons* 191: 479-489. [Crossref]
46. Santini E, Schiavo R, Gucciardo G, Tersigni R, Mango L (2000) Radiation exposure in different RGS procedures.*Q J Nucl Med* 44: 13.
47. Sarri AJ, Tinois da Silva E, Aloisio da Costa Vieira R, Hiromoto Koga K, Moriguchi PE, et al. (2017) Lymphoscintigraphy detecting alterations of upper limb lymphatic flow following early sentinel lymph node biopsy in breast cancer breast cancer. *Breast Cancer (Dove Med Press)* 9 279-285. [Crossref]
48. Johnson TM, Sandok VK, BichaKJian CK, Sabel MS (2006) The role of sentinel lymph node biopsy for melanoma: evidence assessment. *J Am Acad Dermatol* 54:19-27. [Crossref]
49. Manca G, Romanini A, Pellegrino D (2008) Optimal detection of sentinel lymph node metastases by intraoperative radiocative threshold and molecular analysis in patients with melanoma. *J Nucl Med* 49: 1769-1775.
50. Mariani G, Erba P, Villa G (2004) Radioguided sentinel lymph node biopsy in patients with malignant cutaneous melanoma: The nuclear medicine contribution. *J Surg Oncol* 85:141-151.[Crossref]
51. Mango L, Ventroni G (2017) Hybrid Tecnology: From cars to diagnosis. *ARC J Rad Med Imag* 2:1-6.
52. Niikura H, Okamura C, Utsunomiya H, Yoshinaga K, Akahira J, et al. (2004) Sentinel lymph node detection in patients with endometrial cancer. *Gynecol Oncol* 92: 669-674. [Crossref]
53. Di Stefano AB, Acquaviva G, Garozzo G, Barbic M, Cvjeticanin B, et al. (2005) Lymph node mapping and sentinel node detection in patients with cervical carcinoma: a 2-year experience. *Gynecol Oncol* 99: 671-679.[Crossref]
54. Dhar KK, Woolas RP (2005) Lymphatic mapping and sentinel node biopsy in early vulvar cancer. *Gynecol Oncol* 112: 696-702.[Crossref]
55. Wawroschek F, Vogt H, Wengenmair H, Weckermann D, Hamm M, et al. (2003) Prostate lymphoscintigraphy and radio-guided surgery for sentinel lymph node identification in prostate cancer. *Urologia internationalis* 70: 303-310.
56. Liedberg F, Chebil G, Davidsson T, Gudjonsson S, Månsson W (2006) Intraoperative sentinel node detection improves nodal staging in invasive bladder cancer. *The Journal of urology* 175: 84-88.
57. Alvarez Amézaga J, Barbier Herrero L, Pijoan del Barrio JI, Martín Rodríguez JC, Romo Simón L, et al. (2007) Diagnostic efficacy of sentinel node biopsy in oral squamous cell carcinoma. Cohort study and meta-analysis. *Med Oral Patol Oral Cir Bucal* 12: E235-243.[Crossref]
58. Paleri V, Rees G, Arullendran P, Shoaib T, Krishman S (2005) Sentinel node biopsy in squamous cell cancer of the oral cavity and oral pharynx: a diagnostic meta-analysis. *Head Neck* 27: 739-747.[Crossref]
59. Takeuchi H, Kitagawa Y (2016) Minimally invasive function-preserving surgery based on sentinel node concept in early gastric cancer. *Transl Gastroenterol Hepatol* 1: 23.[Crossref]
60. Little AG, DeHoyos A, Kirgan DM, Arcomano TR, Murray KD(1999) Intraoperative lymphatic mapping for non-small cell lung cancer: the sentinel node technique. *J Thorac Cardiovasc Surg* 117: 220-224.[Crossref]
61. Zarifmahmoudi L, Krag DN, Sadeghi R, Bagheri R, Shafi S (2016) Radioguided sentinel lymph nodemapping and biopsy in non-smallcell lung cancer (NSCLC), in K. Herrmann et al. (eds.), Radioguided Surgery: Current Applications and InnovativDirections in Clinical Practice Springer International Publishing Switzerland.