

Time frame of sentinel node visualization in early breast cancer patients using intradermal injection of Tc-99m phytate: Imaging beyond 45 minutes does not yield more information

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ABSTRACT

Introduction: One of the major problems of lymphoscintigraphy is the time of patient presence in the nuclear medicine wards. The operating room schedule can be compromised if the patients stay longer than usual in the nuclear medicine departments. However, too early imaging can be falsely negative for sentinel node visualization and delayed imaging may be required. The aim of the current study is to determine a time beyond which lymphoscintigraphy imaging does not yield more information and imaging can be terminated.

Methods: One hundred and fifty women with proven clinically axillary node negative breast cancer entered the study. For each patient 0.5 mCi Tc-99m phytate in the 0.2 cc volume was intradermally injected in periareolar region to raise a wheal. Lymphoscintigraphy imaging was done in the following time intervals: 5, 10, 30, 45, 60, 90 minutes post injection. In case of sentinel node visualization at any time, the imaging was terminated.

Results: Sentinel nodes were first detected on 5, 10, 30, 45, 60, and 90 minute images in 31 (20.6%), 45 (30%), 46 (30.6%), 15 (10%), 1 (0.6%), and 0 patients. Median number of the detected sentinel nodes per patient was 1. At least one hot sentinel node could be identified in all 138 patients with observed sentinel nodes of whom, 45 had pathologically involved sentinel nodes and axillary lymph node dissection was done. In 12 patients, no sentinel node was visualized even on the 90 minute images. All of these patients had axillary node involvement and no sentinel node could be harvested intra-operatively either.

Conclusion: Considering the rather slow movement of Tc-99m phytate in the lymphatic system, lymphoscintigraphy imaging of the breast cancer patients should be continued for 45 minutes in case of sentinel node detection failure. On the other hand imaging beyond 45 minutes does not seem to be necessary as the diagnostic yield is very low.

Key words: Phytate; Particle size; Breast cancer; Lymphoscintigraphy; Delayed imaging

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INTRODUCTION

Sentinel lymph node mapping is the standard method for axillary staging in early breast cancer patients which can decrease the morbidity of complications of breast cancer surgery [1-6]. Sentinel node mapping is an evolving procedure in surgical oncology and has been applied to almost all solid tumors such as gynecologic, urologic, skin tumors, etc. In addition to breast cancer, lymphatic mapping is gaining acceptance for lymphatic mapping in various solid tumors too [7-14].

Imaging of the lymphatics and sentinel nodes (lymphoscintigraphy) has also been integrated in to the lymphatic mapping procedure. In addition to the location of the sentinel nodes, lymphoscintigraphy can predict intra-operative sentinel node mapping failure [15, 16]. In case of sentinel node non-visualization on lymphoscintigraphy images, intra-operative blue dye injection should also be strongly considered [17, 18].

One of the major problems of lymphoscintigraphy is the time of patient presence in the nuclear medicine wards. The operating room schedule can be compromised if the patients stay longer than usual in the nuclear medicine departments and lymphoscintigraphy imaging should be terminated as soon as possible. However, too early imaging can be falsely negative for sentinel node visualization and delayed imaging may be required [19-21]. Delayed imaging beyond a certain time may not be necessary and would only delay the patient transfer to the operating theater [22]. However, the velocity of lymphatic mapping material in the lymphatic system is dependent on the particle size of the radiotracer, and depth of injection [23-26].

In our country, many center use Tc-99m phytate for sentinel node mapping for which time frame of sentinel node visualization has not been determined [20]. The aim of the current study is to determine a time beyond which lymphoscintigraphy imaging does not yield more information and imaging can be terminated.

METHODS

One hundred and fifty women with proven clinically axillary node negative breast cancer entered the study (Jan 2014 to Jan 2017). All patients were scheduled to undergo surgery the same day of radiotracer injection. For each patient 0.5 mCi Tc-99m-phytate in the 0.2 cc volume was injected in periareolar region intradermally to raise a wheal. Gentle massage was applied to the injection site for 30 seconds in each patient.

Lymphoscintigraphy imaging was done using a variable angle dual head gamma camera in anterior and lateral views (Tc-99m photopeak, 128×128 matrix, low energy high resolution collimator, 5

min/image sets). Timing of imaging was as follows 5, 10, 30, 45, 60, 90 minutes post injection. In case of sentinel node visualization at any time, the imaging was terminated [27].

Lymphoscintigraphy images were evaluated blindly by two experienced nuclear medicine specialists for number and location of sentinel nodes, and lymphatics.

Sentinel nodes were sought intra-operatively using a portable gamma probe (Europrobe, France). Sentinel nodes were pathologically assessed by frozen section. Axillary dissection was not performed for patients with negative frozen section samples.

RESULTS

Overall 150 early breast cancer patients were included with the mean age of 56±21 years. Demographic data of the included patients is shown in Table 1. At least one sentinel node could be identified in 92% (138) of the patients.

Table 1: Demographic data of the included patients.

Total number of patients		150
Age		56±21
Tumor histology	Invasive ductal	95
	Invasive lobular	45
	Other	10
Tumor location	Upper outer	62
	Upper inner	30
	Lower outer	21
	Lower inner	11
	Central	26
Size of the tumor (cm)		2±1.8
History of excisional biopsy	No	14
	Yes	136
Time of first sentinel node visualization	5	31
	10	45
	30	46
	45	15
	60	1
	90	0
	Not visualized	12

Sentinel nodes were first detected on 5, 10, 30, 45, 60, and 90 minute images in 31 (20.6%), 45 (30%), 46 (30.6%), 15 (10%), 1 (0.6%), and 0 patients (Figure 1 and 2). Median number of the detected sentinel nodes per patient was 1 (1-3 sentinel nodes in each patient). At least one hot sentinel node could be identified in all 138 patients with observed sentinel nodes of whom, 45 had pathologically involved sentinel nodes and axillary lymph node dissection was done.

In 12 patients, no sentinel node was visualized even on the 90 minute images. All of these patients had axillary

node involvement and no sentinel node could be harvested intra-operatively either.

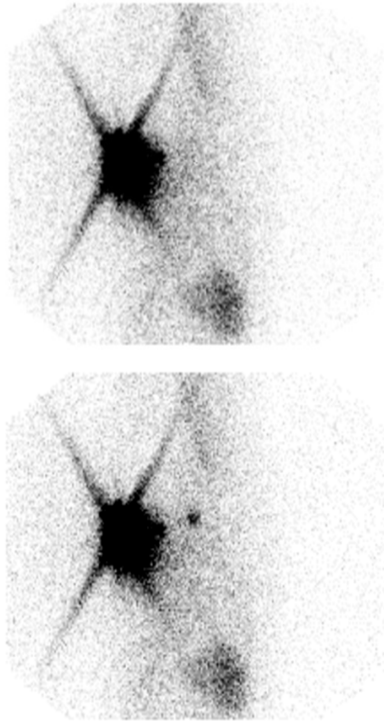


Fig 1. Early (5 min, above) and delayed (30 min, below) left lateral lymphoscintigraphy of a patient. Note sentinel node visualization at 30 minute post injection.

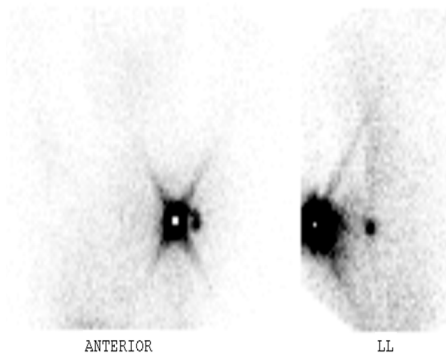


Fig 2. Early (5 min) anterior and lateral lymphoscintigraphy images of another patient. Note the visualization of the sentinel node in these early images.

DISCUSSION

Sentinel node mapping as the standard procedure for axillary lymph node staging is being used in many surgical oncology centers worldwide including many centers in our country [20, 28, 29]. Speed of

radiotracer movement in the lymphatic system is largely determined by the size of the radiotracer particles, and depth of injection. Superficial injection and small particle size hasten the radiotracer movement in the lymphatic system [30, 31]. In our previous study using Tc-99m-antimony sulfide colloid, we have shown very rapid movement of the tracer in the lymphatic system and sentinel nodes were identified on the immediate lymphoscintigraphy imaging in more than 73% of the patients. Actually imaging beyond 30 minutes didn't yield any additional information or increase the detection rate [32]. Other reports of our center also concur with these results and most patients had rapid visualization of sentinel nodes [19, 32].

However, in the current study we used a different radiotracer with larger particle size: Tc-99m phytate. The particle size of Tc-99m antimony sulfide colloid is less than 20 nm. On the other hand the particle size of Tc-99m phytate has particle size of 150 nm and more [26, 33]. This is the reason of delayed sentinel node visualization in most patients in the current study. More than 40% of the patients had their sentinel node visualized after 30 minutes post radiotracer injection. These results show that imaging may be prolonged in lymphoscintigraphy imaging using Tc-99m phytate.

This should be kept in mind especially in patients who are scheduled for the same day protocol (injection and surgery in a same day) in order not to interfere with the operating room schedule. Considering the comparable efficacy and success in same and two day protocols [16, 21, 34], we recommend two day protocol (injection and surgery in two consecutive days) for sentinel node mapping using Tc-99m phytate (even 45 minutes imaging can interfere with operation room scheduling). In case of same day protocol, should the sentinel node is not visualized on the early images, imaging needs to be continued for 45 minutes post injection.

On the other hand, our study also showed that imaging beyond 45 minutes does not yield additional information regarding sentinel node visualization as only in one patient, sentinel node was first seen on 90 minute lymphoscintigraphy.

CONCLUSION

Considering the rather slow movement of Tc-99m phytate in the lymphatic system, lymphoscintigraphy imaging of the breast cancer patients should be continued for 45 minutes in case of sentinel node detection failure. On the other hand imaging beyond 45 minutes does not seem to be necessary as the diagnostic yield is very low. Beyond 45 minutes, sentinel node non-visualization is most likely due to axillary node involvement.

REFERENCES

1. Nathanson SD, Grogan JK, DeBruyn D, Kapke A, Karvelis K. Breast cancer sentinel lymph node identification rates: the influence of radiocolloid mapping, case volume, and the place of the procedure. *Ann Surg Oncol*. 2007 May;14(5):1629-37.
2. Newman EA, Newman LA. Lymphatic mapping techniques and sentinel lymph node biopsy in breast cancer. *Surg Clin North Am*. 2007 Apr;87(2):353-64, viii.
3. Newman LA. Lymphatic mapping and sentinel lymph node biopsy in breast cancer patients: a comprehensive review of variations in performance and technique. *J Am Coll Surg*. 2004 Nov;199(5):804-16.
4. Zarifmahmoudi L, Shabahang H, Shariati F, Dabbagh Kakhki VR, Mehrabibahar M, Sadat Alavifard R, Jangjoo A, Sadeghi R. Dynamic lymphoscintigraphy in breast cancer patients: feasibility and added value. *Iran J Nucl Med*. 2016;24(2):130-5.
5. Kim CK, Zukotynski KA. Desirable Properties of Radiopharmaceuticals for Sentinel Node Mapping in Patients With Breast Cancer Given the Paradigm Shift in Patient Management. *Clin Nucl Med*. 2017 Apr;42(4):275-279.
6. Bromham N, Schmidt-Hansen M, Astin M, Hasler E, Reed MW. Axillary treatment for operable primary breast cancer. *Cochrane Database Syst Rev*. 2017 Jan 4;1:CD004561.
7. Kadkhodayan S, Hasanazadeh M, Treglia G, Azad A, Yousefi Z, Zarifmahmoudi L, Sadeghi R. Sentinel node biopsy for lymph nodal staging of uterine cervix cancer: a systematic review and meta-analysis of the pertinent literature. *Eur J Surg Oncol*. 2015 Jan;41(1):1-20.
8. Hassanzade M, Attaran M, Treglia G, Yousefi Z, Sadeghi R. Lymphatic mapping and sentinel node biopsy in squamous cell carcinoma of the vulva: systematic review and meta-analysis of the literature. *Gynecol Oncol*. 2013 Jul;130(1):237-45.
9. Ansari M, Rad MA, Hassanzadeh M, Gholami H, Yousefi Z, Dabbagh VR, Sadeghi R. Sentinel node biopsy in endometrial cancer: systematic review and meta-analysis of the literature. *Eur J Gynaecol Oncol*. 2013;34(5):387-401.
10. Sadeghi R, Gholami H, Zakavi SR, Kakhki VR, Tabasi KT, Horenblas S. Accuracy of sentinel lymph node biopsy for inguinal lymph node staging of penile squamous cell carcinoma: systematic review and meta-analysis of the literature. *J Urol*. 2012 Jan;187(1):25-31.
11. Sadeghi R, Tabasi KT, Bazaz SM, Kakhki VR, Massoom AF, Gholami H, Zakavi SR. Sentinel node mapping in the prostate cancer. Meta-analysis. *Nuklearmedizin*. 2011;50(3):107-15.
12. Dabbagh Kakhki VR, Bagheri R, Tehranian S, Shojaei P, Gholami H, Sadeghi R, Krag DN. Accuracy of sentinel node biopsy in esophageal carcinoma: a systematic review and meta-analysis of the pertinent literature. *Surg Today*. 2014 Apr;44(4):607-19.
13. Bagheri R, Naghavi F, Dabbagh Kakhki VR, Zakavi SR, Fattahi AS, Jafarian AH, Haghi SZ, Sadeghi R. Sentinel node mapping in esophageal squamous cell carcinoma using intra-operative combined blue dye and radiotracer techniques. *Esophagus*. 2013;10(4):211-6.
14. Taghizadeh Kermani A, Bagheri R, Tehranian S, Shojaei P, Sadeghi R, N Krag D. Accuracy of sentinel node biopsy in the staging of non-small cell lung carcinomas: systematic review and meta-analysis of the literature. *Lung Cancer*. 2013 Apr;80(1):5-14.
15. Lawson LL, Sandler M, Martin W, Beauchamp RD, Kelley MC. Preoperative lymphoscintigraphy and internal mammary sentinel lymph node biopsy do not enhance the accuracy of lymphatic mapping for breast cancer. *Am Surg*. 2004 Dec;70(12):1050-5; discussion 1055-6.
16. Sadeghi R, Forghani MN, Memar B, Abdollahi A, Zakavi SR, Mashhadi MT, Raziiee HR, Tavassoli A, Kakhki VR. Comparison of pre-operative lymphoscintigraphy with inter-operative gamma probe and dye technique regarding the number of detected sentinel lymph nodes. *Hell J Nucl Med*. 2009 Jan-Apr;12(1):30-2.
17. Eldrageely K, Vargas MP, Khalkhali I, Venegas R, Burla M, Gonzalez KD, Vargas HI. Sentinel lymph node mapping of breast cancer: a case-control study of methylene blue tracer compared to isosulfan blue. *Am Surg*. 2004 Oct;70(10):872-5.
18. Sadeghi R, Alesheikh G, Zakavi SR, Fattahi A, Abdollahi A, Assadi M, Jangjoo A, Keshtgar M. Added value of blue dye injection in sentinel node biopsy of breast cancer patients: do all patients need blue dye? *Int J Surg*. 2014;12(4):325-8.
19. Aliakbarian M, Memar B, Jangjoo A, Zakavi SR, Reza Dabbagh Kakhki V, Aryana K, Forghani MN, Sadeghi R. Factors influencing the time of sentinel node visualization in breast cancer patients using intradermal injection of the radiotracer. *Am J Surg*. 2011 Aug;202(2):199-202.
20. Dabbagh Kakhki VR, Jangjoo A, Tavassoli A, Asadi M, Sadri K, Fatahi Masoom A, Mehrabibahar M, Memar B, Ansari M, Sadeghi R. Sentinel node mapping for early breast cancer patients using 99mTc-phytate: Single center experience on 165 patients. *Iran J Nucl Med*. 2012;20(2):25-9.
21. Jangjoo A, Forghani MN, Mehrabibahar M, Rezapana A, Kakhki VR, Zakavi SR, Ghavamnasiri MR, Kashani I, Hashemian F, Sadeghi R. Comparison of early and delayed lymphoscintigraphy images of early breast cancer patients undergoing sentinel node mapping. *Nucl Med Commun*. 2010 Jun;31(6):521-5.
22. Sadeghi R, Forghani MN, Memar B, Rajabi Mashhadi MT, Dabbagh Kakhki VR, Abdollahi A, Zakavi SR. How long the lymphoscintigraphy imaging should be continued for sentinel lymph node mapping? *Ann Nucl Med*. 2009 Aug;23(6):507-10.
23. Mehrabibahar M, Azizi S, Jangjoo A, Saremi E, Kakhki VR, Sadeghi R, Chicken DW, Keshtgar M. Concordance between peri-areolar blue dye and peri-incisional radiotracer injections for sentinel node mapping in patients with a history of primary breast cancer excisional biopsy. *Acta Chir Belg*. 2014 Jan-Feb;114(1):31-3.
24. Sadeghi R, Asadi M, Treglia G, Zakavi SR, Fattahi A, Krag DN. Determining axillary concordance rate for different injection locations in sentinel node mapping of breast cancer: how ambitious can we get? *Breast Cancer Res Treat*. 2014 Jul;146(1):231-2.
25. Sadeghi R, Asadi M, Treglia G, Zakavi SR, Fattahi A, Krag DN. Axillary concordance between superficial and deep sentinel node mapping material injections in breast cancer patients: systematic review and meta-analysis of the literature. *Breast Cancer Res Treat*. 2014 Apr;144(2):213-22.
26. Higashi H, Natsugoe S, Uenosono Y, Ehi K, Arigami T, Nakabeppu Y, Nakajo M, Aikou T. Particle size of tin and phytate colloid in sentinel node identification. *J Surg Res*. 2004 Sep;121(1):1-4.

27. Momennezhad M, Zakavi SR, Dabbagh Kakhki VR, Jangjoo A, Ghavamnasiri MR, Sadeghi R. Scatterogram: a method for outlining the body during lymphoscintigraphy without using external flood source. *Radiol Oncol.* 2011 Sep;45(3):184-8.
28. Moghimi M, Ghoddosi I, Rahimabadi AE, Sheikhatan M. Accuracy of sentinel node biopsy in breast cancer patients with a high prevalence of axillary metastases. *Scand J Surg.* 2009;98(1):30-3.
29. Eftekhari M, Beiki D, Fallahi B, Arabi M, Memari F, Gholamrezanezhad A, Esmaili J, Akhzari F, Fard-Esfahani A. Assessment the diagnostic accuracy of sentinel lymph nodes lymphoscintigraphy using Technetium-99m phytate in breast cancer. *DARU J Pharma Sci.* 2009;17(2):83-7.
30. Imoto S, Murakami K, Ikeda H, Fukukita H, Moriyama N. Mammary lymphoscintigraphy with various radiopharmaceuticals in breast cancer. *Ann Nucl Med.* 1999 Oct;13(5):325-9.
31. Jinno H, Ikeda T, Matsui A, Kitagawa Y, Kitajima M, Fujii H, Nakamura K, Kubo A. Sentinel lymph node biopsy in breast cancer using technetium-99m tin colloids of different sizes. *Biomed Pharmacother.* 2002;56 Suppl 1:213s-216s.
32. Abdollahi A, Jangjoo A, Dabbagh Kakhki VR, Rasoul Zakavi S, Memar B, Naser Forghani M, Mehrabibahar M, Sadeghi R. Factors affecting sentinel lymph node detection failure in breast cancer patients using intradermal injection of the tracer. *Rev Esp Med Nucl.* 2010 Mar-Apr;29(2):73-7.
33. Tsopelas C. Particle size analysis of (99m)Tc-labeled and unlabeled antimony trisulfide and rhenium sulfide colloids intended for lymphoscintigraphic application. *J Nucl Med.* 2001 Mar;42(3):460-6.
34. Ali J, Alireza R, Mostafa M, Naser FM, Bahram M, Ramin S. Comparison between one day and two days protocols for sentinel node mapping of breast cancer patients. *Hell J Nucl Med.* 2011 Sep-Dec;14(3):313-5.