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Breast Cancer and Internal Mammary Sentinel Nodes: A Meta-Analysis

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ABSTRACT

Background: The management of internal mammary (IM) nodes in breast cancer lacks a well-defined consensus. Lymphoscintigraphy identifies up to one-third of breast cancer patients with extra-axillary drainage, which is mainly located in the IM chain.Our aim in this meta-analysis is to identify the lymphoscintigraphy technique variables that effect IM node identification.

Methods: An internet database was utilized to review articles concerning sentinel nodes and breast cancer from 1993 through the end of 2011; 74 articles met our inclusion criteria. The total number of patients included was 22959. We grouped the citations by injection location and injection material. We then analyzed the rate of identification of IM nodes according to these groupings and their subsets.

Results: The overall IM identification rate using the random effect model was 9%. The injection location had the most significant impact on IM identification rate; the deeper injections were associated with the highest rate of identification. Variation in IM identification was associated with the particle size of injection material; the smaller particle size group had a higher rate of identification. Increased dose of the tracer was also associated with increased identification rate.

Conclusions: The use of smaller particle size tracers and a deeper injection location achieve the highest IM identification rate. The dose of the tracer also increased theidentification rate. These observations can help in the selection of patients for IM sentinel node biopsy, which can affect their prognosis and treatment management.

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Introduction

The pathological status of internal mammary (IM) nodes is integral to the tumor node metastasis (TNM) staging of breast cancer.[1] The presence of pathologically positive IM nodes is associated with increased recurrence rate and decreased survival rate regardless of axillary node status. The incidence of IM metastases is up to 33%[2-5] Using

lymphoscintigraphy, extrain-axillary drainage is seen up to one-third of the patients, most frequently to the IM chain.[2,6-8] Management of IM nodes in breast cancer lacks a well-defined consensus, and the multiple methods used for sentinel node (SN) surgery result in a wide variation in the visualization rates of extra-axillary lymph nodes.[3-5] The objective of this meta-analysis is to define the rate of IM Sns associated with the different methods used to detect IM SNs.

Methods

Search strategy

An information service that manages biomedical publications (www.treeofmedicine.com) was used that provides detailed information on 3829 PubMed articles on SNs and breast cancer published between 1993 through 2011. Of the 3829 articles, 218 were categorized as having reported extra-axillary lymph node drainage. These 218 articles were reviewed for inclusion in this meta-analysis. A PubMed search was also performed for review articles and meta analyses related to SN biopsy in breast cancer and extra-axillary drainage.

Selection criteria

Articles had to document drainage to IM SNs for a group of patients and specify the injection location(s) and tracer(s) for that group. Articles that reported results largely based on the same group of patients cited in another article were excluded. Articles that were not available in English were also excluded.

Data collection

Patients were grouped according to the injection location and the tracers used. Tracers included ^{99m}Tc tagged nanocolloid, sulfur colloid (TSC), tin colloid, phytate, dextran, antimony sulfide, rhenium colloid, large albumin particles (Senti- Scint or Albu/Res), human albumin serum (HAS), human polyclonal immunoglobulin G (HIG), and methoxyisobutylisonitrile (MIBI). The tracers were further classified according to their particle size. Tracers with a particle size larger than 200 nm were classified as large and included Senti-Scint, Alb-Res, tin colloid, and phytate. Tracers with a particle size smaller than 200 nm and greater than 3 nm were classified as small and included nanocolloid, filtered sulfur colloid, antimony sulfide, and rhenium sulfide. Tracers with a particle size smaller than 3 nm were classified as very small and included dextran, HIG, and MIBI. Unfiltered TSC has a range of particle sizes that cross our classification scheme and was thus classified as a fourth group. The injection location was classified as: 1) around the tumor (including subcutaneous over the tumor); 2) subtumoral; 3) areolar or periareolar; 4) intratumoral; 5) subdermal; and 6) intradermal injections. Combinations were classified as: 1) deep, including sub-tumoral injection, around the tumor, intratumoral injection, and any combination that included these three locations; and 2) superficial, including intra-dermal, areolar, and sub-dermal injections, and any combination of intra-dermal or sub-dermal locations.

With respect to pathologically positive IM nodes, 26 articles met the inclusion criteria, where the number of IM nodes identified on lymphoscintigraphy and the number of pathologically positive IM nodes were clearly stated. Due to the limited number of articles we were not able to sufficiently analyze the pathological data in relation to injection material and location.

Statistical analysis

For each study, we calculated the proportion of cases with IM drainage, with or without axillary drainage, identified by lymphoscintigraphy. The arc sine of the square root of this proportion was utilized for the meta-analysis, while the inverse transformation was utilized to obtain summary effect size estimates and 95% confidence intervals in the original IM drainage rate scale for ease of interpretation.[9] Each covariate was examined relative to variation among the transformed drainage rate data with the use of a mixed model. Forest plots of the inverse transformed IM or isolated IM (ISIM) drainage rate data were calculated for those covariate groups with significant mixed model statistical heterogeneity based on the Q-test.[10] This was followed with pair-wise comparisons to isolate the source of the drainage rate heterogeneity. To evaluate the effect of tracer dose on IM identification, a meta-regression was implemented where IM and ISIM rates were examined as a function of mean dose within some tracers that had a sufficient number of citations. To evaluate the rate of pathologically positive IM nodes, we used random effect model to report the overall IM rate identified in these articles and IM positive rates in those IM nodes identified. All primary data transformations, back transformations, and recoding were conducted using SYSTAT for Windows (version 11; Systat Software Inc., Chicago, IL, USA). All meta-analysis calculations and graphical displays were obtained using Comprehensive Meta-Analysis (version 2.2; Biostat Inc., Englewood, NJ, USA).

Results

Of 218 articles that reported IM node visualization, 73 articles met the inclusion criteria.[11-83] Of the included articles, 42 also reported ISIM visualization. In addition, 24 articles had 2 or more mutually exclusive patient groups. This yielded 108 unique patient groups for analysis of overall IM visualization and 54 for ISIM. The total number of patients was 22959. The total number of patients with

IM visualization was 3194. The crude overall IM rate was 13.9% (CI: 13.5-14.4%) and 9.0% (CI: 7.2-10.9%) using a random effects model. The total number of patients in the articles that reported ISIM visualization was 11999, of which 176 patients had ISIM imaged. The crude overall ISIM rate was 1.5% (CI: 1.3-1.7%). The overall ISIM rate using a random effects model was 0.9% (0.5-1.4%).

By tracer utilized

The IM node visualization rates showed a significant difference between the large, small, and very small particle size groups (Q = 7.92, df = 2, P = 0.02). The rate of IM visualization was 4.0% (CI: 1.4-7.8%) for the large, 9.8% (CI: 7.8-12%) for the small, and 16.6% (CI: 5-33%) for the very small categories. The rate of ISIM visualization was, respectively, 0.1% (CI: 0.0-0.8%), 1.2% (CI: 0.6 2%), and 10% (CI: 1-27%); these differences were significant (Q = 9.77, df = 2, P = 0.008). When adding TSC to the analysis, the overall difference between the groups remained statistically significant for the IM rate (Q = 7.97, df = 3, P = 0.046) and the ISIM rate (Q = 10, df = 3, P = 0.02). TSC had an IM rate of 9.7% (CI: 4-17%) and an ISIM rate of 0.5% (CI: 0.04-1.6%). Subsequent paired comparisons between these four categories showed significant differences between the small and large categories in IM visualization rate (P > 0.001), and between the large and very small categories (P = 0.04). Comparison of the small and very small categories did not show a significant difference (P = 0.3). TSC did not show a significant difference between any of the other 3 categories (all P values > 0.1). Interestingly, in the paired comparisons for the ISIM rate, TSC showed a significant difference in the very small category (P = 0.03) but did not show any difference in the large or small categories with P values > 0.25 (Figure 1).

We then compared the IM and ISIM rate of the tracers within each group (Figure 2). The IM rate had no significant variation between tracers in the very small category (Q = 0.34, df = 3, P = 0.85) and in the small size category (Q = 2.3, df = 3, P = 0.51). However, in the large size group there was a significant group difference between the 4 tracers utilized (Q = 10.43, df = 3, P = 0.015). There was no significant variation in ISIM rate when comparing individual tracers within either the small group (P = 0.8) or the large group (P = 0.3). Analysis of tracers was not possible for the very small group as there was only one citation.

In the large particle category the IM rate for Albu-Res of 14.3% (CI: 8.6-21.1%) was significantly higher than Phytate at 3.4% (CI: 0.3-9.8%) (P = 0.01) and Senti-Scint at 2.7% (CI: 0.03-9.6%) (P = 0.01), and marginally higher than tin colloid at 4.1% (CI: 0.05 14%) (P = 0.07). The remaining paired analysis between the other tracers within this group showed no significant difference (all P values > 0.35).

Controlling the injection location, we analyzed the impact of particle size on IM visualization. We used the 51 citations with injection locations around the tumor, since this was the most frequently used location (Figure 3). The overall group differences and the paired comparison between the particle size groups showed a similar relationship to that observed in the analysis that included all injection locations with respect to IM rates. However, for the ISIM rate there was only a marginal difference between the small and the large categories (P = 0.06). The IM rate for TSC was not significantly different from any of the other 3 categories (all P values > 0.1).

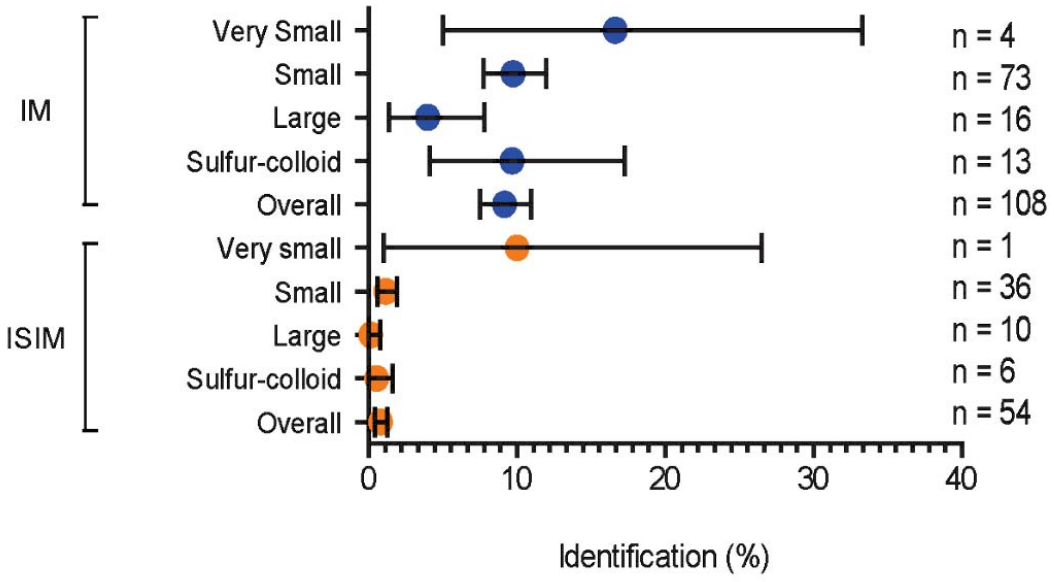

Figure 1. Forest plot showing the rate of IM and ISIM visualization according to particle size category

(N = number of citations utilizing the corresponding category)

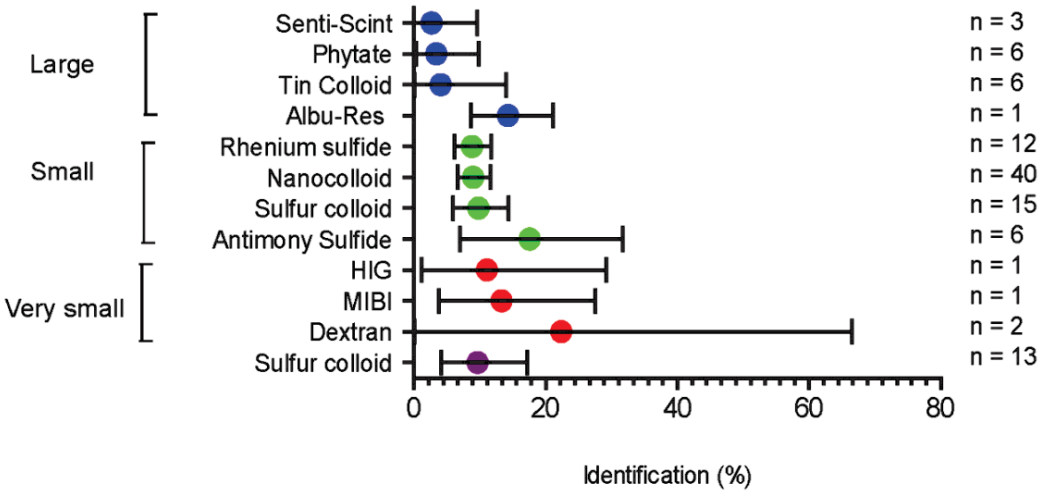

Figure 2. Forest plot showing the rate of IM visualization for the individual tracers grouped according to particle size (N = number of citations utilizing the corresponding tracer)

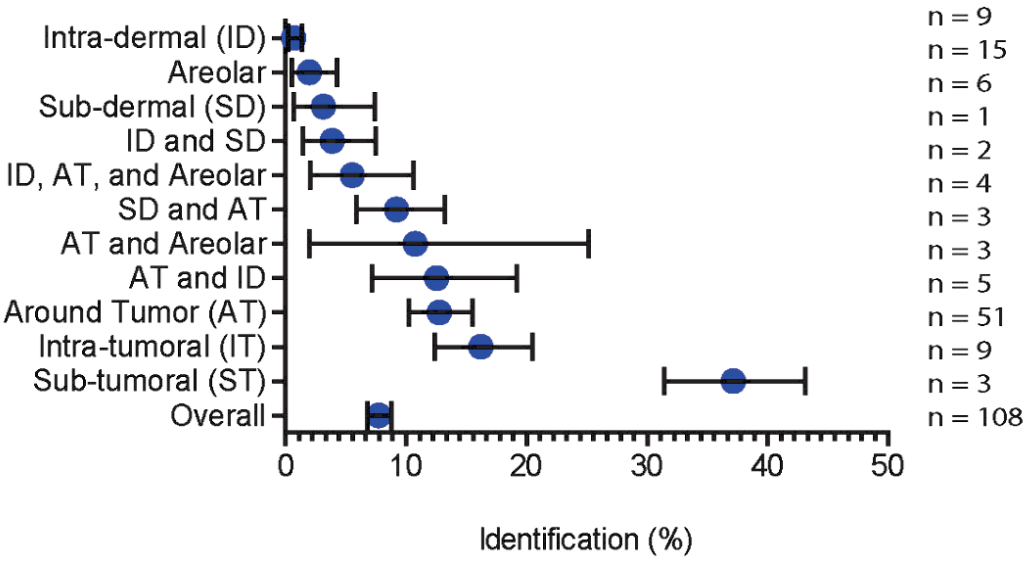

Figure 3. Forest plot showing the rate of IM and ISIM visualization according to particle size category with the injection location of around the tumor (N = number of citations utilizing the corresponding category)

By location of injection

There were 11 categories according to injection location. When comparing the IM rate for all the injection locations included in the analysis, we observed a significant group difference among them ($Q = 334.4$, $df = 10$, $P < 0.001$) (Figure 4). Comparison of the 6 categories with single injection locations, still showed a significant group difference among them ($Q = 325.3$, $df = 5$, $P < 0.001$). Subsequent paired comparisons between the single injection locations showed the sub-tumoral location, with the highest rate of IM visualization at 37.2% (CI: 31.4-43%), was significantly different from all other single injection locations ($P < 0.001$). The around the tumor location at 12.8% (CI: 10.2-15.5%) was not significantly different from the intra tumoral location at 16.2% (CI: 12.4-20.5%) ($P = 0.16$), while these two locations were significantly different from areolar at 2% (CI: 0.5-4.3%) subdermal at 3.2% (CI: 0.7-7.5%), and intradermal locations at 0.7% (CI: 0.2-1.4%) ($P < 0.001$). No significant differences were observed among the latter 3 locations on the paired comparisons (all P values > 0.05). The overall group differences and the paired comparisons between the injection locations with respect to ISIM visualization rates showed a similar relationship to that observed for the IM visualization rates. The details of this data are not presented in this manuscript.

The rate of IM visualization for the superficial group was 1.7% (CI: 0.9-2.8%) and for the deep group 13.4% (CI: 11.4-15.5%) ($P < 0.001$). The ISIM rate was 0.2% (CI: 0.0-0.8%) for the superficial group and 1.3% (CI: 0.7-2%) for the deep group ($P = 0.008$).

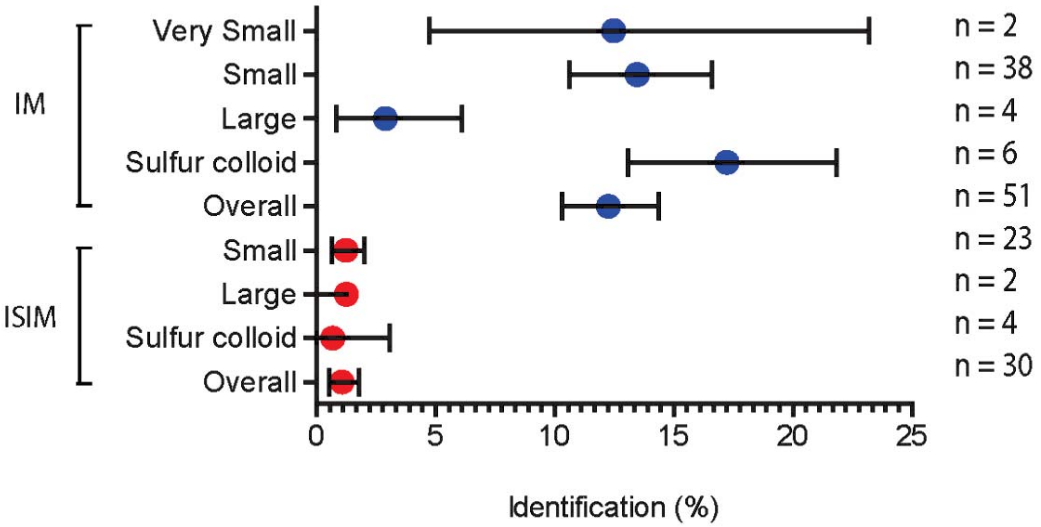

Figure 4. Forest plot showing the rate of IM visualization according to the injection location (N = number of citation utilizing the corresponding injection location)

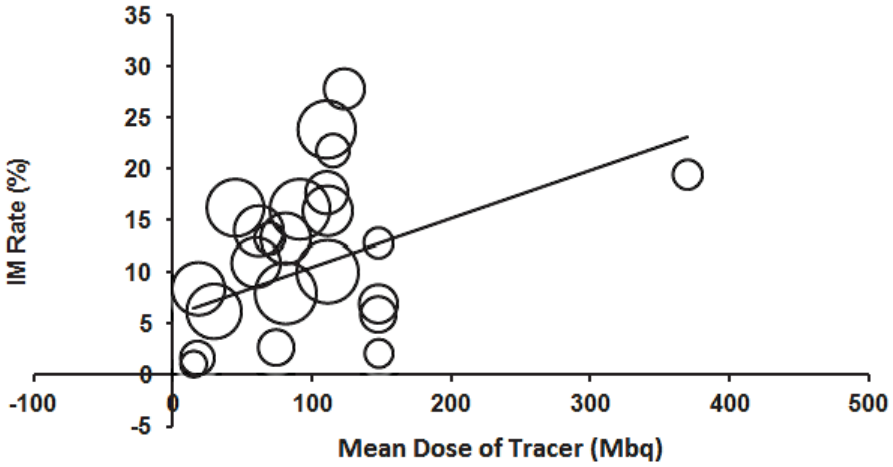

Figure 5. Sample plot showing the rate of increase of IM visualization as a function of mean dose of tracer utilizing nanocolloid as the tracer (The size of the circle represents the weight of the citation (sample size))

By dose of tracer

Using the linear regression method, the IM identification rate, as a function of mean dose of the tracer, was estimated and plotted for27 citations. A positive slope of 0.42% increase in IM rate for every 10 Mbq increase in dose of tracer was statistically significant ($P < 0.001$). The slope was slightly larger (0.52%) when removing the outlier with the highest mean dose of 370 Mbq. (Figure5). There was significant variation among the studies with regard to the sample size as is reflected by the differing circled effect sizes.

Pathology

Regarding pathologically positive IM nodes, 26 articles met the inclusion criteria. The overall rate of IM nodes visualized on lymphoscintigraphy in the citations using random effects model is 16.3% (CI: 13.4-19%). The overall rate of IM positive nodes of those identified is 18% (CI: 15.7-20.5%).

Discussion

In this meta-analysis, the rate of IM identificationwas significantly higher in the deep injection group compared to the superficial injection group.Variation in IM lymphatic drainage has also been reported to be related to breast quadrant.[3,5,8] These data indicate that tumors in differing locations and depth in the breast have different rates IM nodes.

This meta-analysis demonstrated a significantly higher rate of visualization of IM nodes in the smaller particle size tracers as compared to the larger particle size. This remained significant even when controlled for a single injection location. Increased flow to lymph nodes due to smaller particle size is consistent with the permeability of lymphatic capillaries.[66,84,85] Moreover, unfiltered sulfur colloid did not demonstrate any difference in the IM rate from that of the other groups. This can be explained by the wide range of particle size of TSC that includes large, small, and very small particles.

This meta-analysis also demonstrated a significant increase in IM node visualization with increasing tracer dose. The radiation exposure hazards from these injections are low and increasing the dose is an option that increases IM node visualization rate.[86] Data regarding the dose of radiotracer are limited and more studies are needed to accurately define the relationship between dose and IM node visualization.

The reported higher frequency of metastases to axillary compared to IM nodes is consistent with greater overall lymphatic flow to the axilla.[7,8,87] When there is IM drainage, the rate of metastases to surgically excised IM SNs is approximately 18%.[3,5] Since the definition of SNs is the nodes receiving direct drainage from a tumor, IM nodes receiving drainage are SNs. Evidence for this is based both on lymphatic mapping to IM nodes and dissemination of cancer cells to IM nodes. We propose that the definition of false negative events not be restricted to axillary nodes but include any SNs. For example, when an axillary SN is negative and there is an IM SN node that is pathologically positive and unresected, this is a false negative event. This proposed definition is more biologically relevant and is not limited to the axilla for calculating the false negative rate. This does not mean that every patient should have an IM node biopsy. Tracer technology allows selection for biopsy of only the minority of patients with documented lymphatic flow to the IM SNs. In those patients having an IM node biopsy, the expectation of morbidity with modern IM SN surgery techniques, unlike extensive resections performed in the past, is very low.[40,50,78,88-90]

The presence of IM metastasis has similar prognostic value to axillary metastasis and can lead to upstaging according to the AJCC guidelines. This can result in treatment changes for both systemic and radiation therapy.[3,4,91,92] Leaving behind IM Sns should also be put in context with the relationship between loco-regional control and improvement of long-term survival that has been demonstrated by the EBCTCG meta-analysis.[93]

The results of this meta-analysis show that the subset of patients observed to have lymphatic drainage to IM SNs varies significantly according to methods. Methods that used deeper injection location and smaller particle size tracers were significantly associated with higher rates of IM SN identification. In addition, a higher dose of tracer was associated with an increase in IM identification rate. These observations can help the selection of patients for IM SN biopsy, which can affect their prognosis and treatment management.[2,3,91,92]

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Conflict of interests

David Krag is the founder of www.TreeofMedicine.com.

References

1. Edge SB. AJCC Cancer Staging Handbook: From the AJCC Cancer Staging Manual. 7th ed. Berlin, Germany: Springer; 2010.
2. Cody HS. Clinical significance and management of extra-axillary sentinel lymph nodes: worthwhile or irrelevant? Surg Oncol Clin N Am 2010; 19(3): 507-17.
3. Chen RC, Lin NU, Golshan M, Harris JR, Bellon JR. Internal mammary nodes in breast cancer: diagnosis and implications for patient management-a systematic review. J Clin Oncol 2008; 26(30): 4981-9.
4. Cserni G, Szekeres JP. Internal mammary lymph nodes and sentinel node biopsy in breast cancer. Surg Oncol 2001; 10(1-2): 25-33.
5. Klauber-DeMore N, Bevilacqua JL, Van Zee KJ, Borgen P, Cody HS. Comprehensive review of the management of internal mammary lymph node metastases in breast cancer. J Am Coll Surg 2001; 193(5): 547-55.
6. Hultborn KA, Larsson LG, Ragnhult I. The lymph drainage from the breast to the axillary and parasternal lymph nodes, studied with the aid of colloidal Au198. Acta radiol 1955; 43(1): 52-64.
7. Sage HH, Gozun BV. Lymphatic scintigrams: a method for studying the functional pattern of lymphatics and lymph nodes. Cancer 1958; 11(1): 200-3.
8. Vendrell-Torne E, Setoain-Quinquer J, Domenech- Torne FM. Study of normal mammary lymphatic drainage using radioactive isotopes. J Nucl Med 1972; 13(11): 801-5.
9. Dixon WJ, Massey FJ. Introduction to Statistical Analysis. 3rd ed. New York, NY: McGraw-Hill; 1969.
10. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to Meta-Analysis. New Jersey, NJ: Wiley; 2009.
11. Rodier JF, Velten M, Wilt M, Martel P, Ferron G, Vaini-Elies V, *et al*. Prospective multicentric randomized study comparing periareolar and peritumoral injection of radiotracer and blue dye for the detection of sentinel lymph node in breast sparing procedures: FRANSENODE trial. J Clin Oncol 2007; 25(24): 3664-9.
12. Roumen RM, Valkenburg JG, Geuskens LM. Lymphoscintigraphy and feasibility of sentinel node biopsy in 83 patients with primary breast cancer. Eur J Surg Oncol 1997; 23(6): 495-502.
13. Rubio I, Pedreira F, Roca I, Cabaleiro A, Mendoza C, Cordoba O, *et al*. Removal of all radioactive sentinel nodes in breast cancer improves the detection of positive sentinel nodes. Clin Transl Oncol 2008; 10(6): 347-50.

14. Shahar KH, Buchholz TA, Delpassand E, Sahin AA, Ross MI, Ames FC, *et al*. Lower and central tumor location correlates with lymphoscintigraphy drainage to the internal mammary lymph nodes in breast carcinoma. Cancer 2005; 103(7): 1323-9.
15. Shimazu K, Tamaki Y, Taguchi T, Motomura K, Inaji H, Koyama H, *et al*. Lymphoscintigraphic visualization of internal mammary nodes with subtumoral injection of radiocolloid in patients with breast cancer. Ann Surg 2003; 237(3): 390-8.
16. Shivers S, Cox C, Leight G, Beauchamp D, Blumencranz P, Ross M, *et al*. Final results of the Department of Defense multicenter breast lymphatic mapping trial. Ann Surg Oncol 2002; 9(3): 248-55.
17. Shoher A, Diwan A, Teh BS, Lu HH, Fisher R, Lucci A. Lymphoscintigraphy does not enhance sentinel node identification or alter management of patients with early breast cancer. Curr Surg 2006; 63(3): 207-12.
18. Solorzano CC, Ross MI, Delpassand E, Mirza N, Akins JS, Kuerer HM, *et al*. Utility of breast sentinel lymph node biopsy using day-before-surgery injection of high-dose 99mTc-labeled sulfur colloid. Ann Surg Oncol 2001; 8(10): 821-7.
19. Somasundaram SK, Chicken DW, Waddington WA, Bomanji J, Ell PJ, Keshtgar MR. Sentinel node imaging in breast cancer using superficial injections: technical details and observations. Eur J Surg Oncol 2009; 35(12): 1250-6.
20. Sun X, Liu JJ, Wang YS, Wang L, Yang GR, Zhou ZB, *et al*. Roles of preoperative lymphoscintigraphy for sentinel lymph node biopsy in breast cancer patients. Jpn J Clin Oncol 2010; 40(8): 722-5.
21. Ting AC, Cumarasingam B, Szeto ER. Successful internal mammary visualization with periareolar injections of Tc-99m antimony sulfur colloid in sentinel node breast lymphoscintigraphy. Clin Nucl Med 2006; 31(10): 593-7.
22. Upponi SS, McIntosh SA, Wishart GC, Balan KK, Purushotham AD. Sentinel lymph node biops y in breast cancer--is lymphoscintigraphy really necessary? Eur J Surg Oncol 2002; 28(5): 479-80.
23. Uren RF, Howman-Giles R, Renwick SB, Gillett D. Lymphatic mapping of the breast: locating the sentinel lymph nodes. World J Surg 2001; 25(6): 789-93.
24. Valdes-Olmos RA, Jansen L, Hoefnagel CA, Nieweg OE, Muller SH, Rutgers EJ, *et al*. Evaluation of mammary lymphoscintigraphy by a single intratumoral injection for sentinel node identification. J Nucl Med 2000; 41(9): 1500-6.
25. Wang L, Yu JM, Wang YS, Zuo WS, Gao Y, Fan J, *et al*. Preoperative lymphoscintigraphy predicts the successful identification but is not necessary in sentinel lymph nodes biopsy in breast cancer. Ann Surg Oncol 2007; 14(8): 2215-20.
26. Watanabe T, Kimijima I, Ohtake T, Tsuchiya A, Shishido F, Takenoshita S. Sentinel node biopsy with technetium-99m colloidal rhenium sulphide in patients with breast cancer. Br J Surg 2001; 88(5): 704-7.
27. Yao MS, Kurland BF, Smith AH, Schubert EK, Dunnwald LK, Byrd DR, *et al*. Internal mammary nodal chain drainage is a prognostic indicator in axillary node-positive breast cancer. Ann Surg Oncol 2007; 14(10): 2985-93.
28. Yararbas U, Argon AM, Yeniay L, Zengel B, Kapkac M. The effect of radiocolloid preference on major parameters in sentinel lymph node biopsy practice in breast cancer. Nucl Med Biol 2010; 37(7): 805-10.
29. Aras G, Arican P, Cam R, Kucuk NO, Ibis E, Tuzuner A, *et al*. Identification of sentinel lymph node in breast cancer by lymphoscintigraphy and surgical gamma probe with peritumoral injection of scintimammographic agent "99mTc MIbI". Ann Nucl Med 2002; 16(2): 121-6.
30. Bajen MT, Benitez A, Mora J, Ricart Y, Ferran N, Guirao S, *et al*. Subdermal re-injection: a method to increase surgical detection of the sentinel node in breast cancer without increasing the false-negative rate. Eur J Nucl Med Mol Imaging 2006; 33(3): 338-43.
31. Birdwell RL, Smith KL, Betts BJ, Ikeda DM, Strauss HW, Jeffrey SS. Breast cancer: variables affecting sentinel lymph node visualization at preoperative lymphoscintigraphy. Radiology 2001; 220(1): 47-53.
32. Borgstein PJ, Meijer S, Pijpers RJ, van Diest PJ. Functional lymphatic anatomy for sentinel node biopsy in breast cancer: echoes from the past and the periareolar blue method. Ann Surg 2000; 232(1): 81-9.
33. Brenot-Rossi I, Houvenaeghel G, Jacquemier J, Bardou VJ, Martino M, Hassan-Sebbag N, *et al*. Nonvisualization of axillary sentinel node during lymphoscintigraphy: is there a pathologic significance in breast cancer? J Nucl Med 2003; 44(8): 1232-7.
34. Carcoforo P, Sortini D, Feggi L, Feo CV, Soliani G, Panareo S, *et al*. Clinical and therapeutic importance of sentinel node biopsy of the internal mammary chain in patients with breast cancer: a single-center study with long-term follow-up. Ann Surg Oncol 2006; 13(10): 1338-43.
35. Chakera AH, Friis E, Hesse U, Al-Suliman N, Zerahn B, Hesse B. Factors of importance for scintigraphic non-visualisation of sentinel nodes in breast cancer. Eur J Nucl Med Mol Imaging 2005; 32(3): 286-93.
36. Chen YW, Lai YC, Hsu CC, Chuang YW, Hou MF. Value of nodal drainage patterns and tumor location from lymphoscintigraphic mapping in

detecting axillary sentinel lymph node status in breast cancer: experience at Kaohsiung Medical University Hospital. Kaohsiung J Med Sci 2005; 21(6): 251-7.
37. Climaco F, Coelho-Oliveira A, Djahjah MC, Gutfilen B, Correia AH, Noe R, *et al*. Sentinel lymph node identification in breast cancer: a comparison study of deep versus superficial injection of radiopharmaceutical. Nucl Med Commun 2009; 30(7): 525-32.
38. Dede F, Gulluoglu BM, Ones T, Farsakoglu Z, Caliskan B, Memis H, *et al*. Multiparametric analysis of preoperative lymphatic mapping with the use of combined deep plus superficial radiotracer injection technique in early breast cancer. Nucl Med Commun 2008; 29(6): 546-52.
39. Doting MH, Stiekema HM, de VJ, Lemstra C, Hoekstra HJ, Vrieling M, *et al*. Immediate dynamic lymphoscintigraphy delivers no additional value to lymphoscintigraphy 3 hr after tracer injection in sentinel lymph node biopsy in breast cancer patients. J Surg Oncol 2007; 95(6): 469-75.
40. Estourgie SH, Tanis PJ, Nieweg OE, Valdes Olmos RA, Rutgers EJ, Kroon BB. Should the hunt for internal mammary chain sentinel nodes begin? An evaluation of 150 breast cancer patients. Ann Surg Oncol 2003; 10(8): 935-41.
41. Feezor RJ, Kasraeian A, Copeland EM, Schell SR, Hochwald SN, Cendan J, *et al*. Sequential dermalperitumoral radiocolloid injection for sentinel node biopsy for breast cancer: the University of Florida experience. Am Surg 2002; 68(8): 684-7.
42. Fernandez A, Escobedo A, Benito E, Azpeitia D, Guma A, Prieto L, *et al*. Sentinel node localization in patients with non-palpable breast cancer. Nucl Med Commun 2002; 23(12): 1165-9.
43. Fleming FJ, Hill AD, Kavanagh D, Quinn C, O'Doherty A, Collins CD, *et al*. Intradermal radioisotope injection optimises sentinel lymph node identification in breast cancer. Eur J Surg Oncol 2003; 29(10): 835-8.
44. Geertsema D, Gobardhan PD, Madsen EV, Albregts M, van Gorp J, de Hooge P, *et al*. Discordance of intraoperative frozen section analysis with definitive histology of sentinel lymph nodes in breast cancer surgery: complementary axillary lymph node dissection is irrelevant for subsequent systemic therapy. Ann Surg Oncol 2010; 17(10): 2690-5.
45. Gencoglu EA, Yalcn H, Yagmurdur M, Ozen A, Basaran O, Karakayal F, *et al*. The efficacy of 99mTc- HIG for sentinel lymph node mapping in breast cancer patients. Nucl Med Commun 2005; 26(9): 781-6.
46. Goyal A, Newcombe RG, Mansel RE, Chetty U, Ell P, Fallowfield L, *et al*. Role of routine preoperative lymphoscintigraphy in sentinel node biopsy for breast cancer. Eur J Cancer 2005; 41(2): 238-43.
47. Guenther JM, Collins JC, Barnes G, O'Connell TX. Selective lymphoscintigraphy: a necessary adjunct to dye-directed sentinel node biopsy for breast cancer? Arch Surg 2000; 135(9): 1101-5.
48. Gutman F, Sanson A, Piquenot JM, Hitzel A, Ladonne JM, Dessogne P, *et al*. Intra-individual comparison of sentinel lymph node scintigraphy on the day of injection and on the following day in breast cancer. Nucl Med Commun 2006; 27(1): 5-9.
49. Haigh PI, Hansen NM, Giuliano AE, Edwards GK, Ye W, Glass EC. Factors affecting sentinel node localization during preoperative breast lymphoscintigraphy. J Nucl Med 2000; 41(10): 1682-8.
50. Heuts EM, van der Ent FW, von Meyenfeldt MF, Voogd AC. Internal mammary lymph drainage and sentinel node biopsy in breast cancer - A study on 1008 patients. Eur J Surg Oncol 2009; 35(3): 252-7.
51. Jangjoo A, Forghani MN, Mehrabibahar M, Rezapanah A, Kakhki VR, Zakavi SR, *et al*. Comparison of early and delayed lymphoscintigraphy images of early breast cancer patients undergoing sentinel node mapping. Nucl Med Commun 2010; 31(6): 521-5.
52. Johnson N, Soot L, Nelson J, Franzini MD, Vea H, Gruner S, *et al*. Sentinel node biopsy and internal mammary lymphatic mapping in breast cancer. Am J Surg 2000; 179(5): 386-8.
53. Kawase K, Gayed IW, Hunt KK, Kuerer HM, Akins J, Yi M, *et al*. Use of lymphoscintigraphy defines lymphatic drainage patterns before sentinel lymph node biopsy for breast cancer. J Am Coll Surg 2006; 203(1): 64-72.
54. Kim R, Osaki A, Kojima J, Toge T. Significance of lymphoscintigraphic mapping with Tc-99m human serum albumin and tin colloid in sentinel lymph node biopsy in breast cancer. Int J Oncol 2001; 19(5): 991-6.
55. Koizumi M, Koyama M, Yamashita T, Tada KI, Nishimura SI, Takahashi K, *et al*. Experience with intradermal injection and intradermal-plus-deep injection in the radioguided sentinel node biopsy of early breast cancer patients. Eur J Surg Oncol 2006; 32(7): 738-42.
56. Krynyckyi BR, Chun H, Kim HH, Eskandar Y, Kim CK, Machac J. Factors affecting visualization rates of internal mammary sentinel nodes during lymphoscintigraphy. J Nucl Med 2003; 44(9): 1387-93.
57. Lamonica D, Edge SB, Hurd T, Proulx G, Stomper PC. Mammographic and clinical predictors of drainage patterns in breast lymphoscintigrams obtained during sentinel node procedures. Clin Nucl Med 2003; 28(7): 558-64.

58. Langer I, Guller U, Berclaz G, Koechli OR, Moch H, Schaer G, *et al*. Accuracy of frozen section of sentinel lymph nodes: a prospective analysis of 659 breast cancer patients of the Swiss multicenter study. Breast Cancer Res Treat 2009; 113(1): 129-36.
59. Lavoue V, Nos C, Clough KB, Baghaie F, Zerbib E, Poulet B, *et al*. Simplified technique of radioguided occult lesion localization (ROLL) plus sentinel lymph node biopsy (SNOLL) in breast carcinoma. Ann Surg Oncol 2008; 15(9): 2556-61.
60. Leidenius MH, Leppanen EA, Krogerus LA, Smitten KA. The impact of radiopharmaceutical particle size on the visualization and identification of sentinel nodes in breast cancer. Nucl Med Commun 2004; 25(3): 233-8.
61. Leidenius MH, Vironen JH, von Smitten KA, Heikkila PS, Joensuu H. The outcome of sentinel node biopsy in breast cancer patients with preoperative surgical biopsy. J Surg Oncol 2009; 99(7): 420-3.
62. Masiero PR, Xavier NL, Spiro BL, Detanico MF, Xavier MC, Pinto AL. Scintigraphic sentinel node detection in breast cancer patients: paired and blinded comparison of 99mTc dextran 500 and 99mTc phytate. Nucl Med Commun 2005; 26(12): 1087-91.
63. Mathew MA, Saha AK, Saleem T, Saddozai N, Hutchinson IF, Nejim A. Pre-operative lymphoscintigraphy before sentinel lymph node biopsy for breast cancer. Breast 2010; 19(1): 28 32.
64. Maza S, Valencia R, Geworski L, Zander A, Guski H, Winzer KJ, *et al*. Peritumoural versus subareolar administration of technetium-99m nanocolloid for sentinel lymph node detection in breast cancer: preliminary results of a prospective intra-individual comparative study. Eur J Nucl Med Mol Imaging 2003; 30(5): 651-6.
65. McCarter MD, Yeung H, Yeh S, Fey J, Borgen PI, Cody HS, III. Localization of the sentinel node in breast cancer: identical results with same-day and day before isotope injection. Ann Surg Oncol 2001; 8(8): 682-6.
66. McMaster PD, Hudack S, Rous P. The relation of hydrostatic pressure to the gradient of capillary permeability. J Exp Med 1932; 55(2): 203-21.
67. Mechella M, De ,Cesare A, Di, Luzio E, Di, Paolo M, Bolognese A, Scopinaro F. A study of sentinel node biopsy in T1 breast cancer treatment: experience of 48 cases. Tumori 2000; 86(4): 320-1.
68. Mirzaei S, Rodrigues M, Hoffmann B, Knoll P, Riegler-Keil M, Kreuzer W, *et al*. Sentinel lymph node detection with large human serum albumin colloid particles in breast cancer. Eur J Nucl Med Mol Imaging 2003; 30(6): 874-8.
69. Molland JG, Dias MM, Gillett DJ. Sentinel node biopsy in breast cancer: results of 103 cases. Aust N Z J Surg 2000; 70(2): 98-102.
70. Mudun A, Sanli Y, Ozmen V, Turkmen C, Ozel S, Eroglu A, *et al*. Comparison of different injection sites of radionuclide for sentinel lymph node detection in breast cancer: single institution experience. Clin Nucl Med 2008; 33(4): 262-7.
71. Nakashima K, Kurebayashi J, Sonoo H, Tanaka K, Ikeda M, Shiiki S, *et al*. Preoperative dynamic lymphoscintigraphy predicts sentinel lymph node metastasis in patients with early breast cancer. Breast Cancer 2010; 17(1): 17-21.
72. Newman EA, Cimmino VM, Sabel MS, Diehl KM, Frey KA, Chang AE, *et al*. Lymphatic mapping and sentinel lymph node biopsy for patients with local recurrence after breast-conservation therapy. Ann Surg Oncol 2006; 13(1): 52-7.
73. Noguchi M, Inokuchi M, Zen Y. Complement of peritumoral and subareolar injection in breast cancer sentinel lymph node biopsy. J Surg Oncol 2009; 100(2): 100-5.
74. Noguchi M, Tsugawa K, Miwa K, Yokoyama K, Nakajima KI, Michigishi T, *et al*. Sentinel lymph node biopsy in breast cancer using blue dye with or without isotope localization. Breast Cancer 2000; 7(4): 287-96.
75. Noushi F, Spillane AJ, Uren RF, Gebski V. Internal mammary node metastasis in breast cancer: predictive models to determine status & management algorithms. Eur J Surg Oncol 2010; 36(1): 16-22.
76. O'Hea BJ, Hill AD, El-Shirbiny AM, Yeh SD, Rosen PP, Coit DG, *et al*. Sentinel lymph node biopsy in breast cancer: initial experience at Memorial Sloan- Kettering Cancer Center. J Am Coll Surg 1998; 186(4): 423-7.
77. Paganelli G, Galimberti V, Trifiro G, Travaini L, De Cicco C, Mazzarol G, *et al*. Internal mammary node lymphoscintigraphy and biopsy in breast cancer. Q J Nucl Med 2002; 46(2): 138-44.
78. Paredes P, Vidal-Sicart S, Zanon G, Pahisa J, Fernandez PL, Velasco M, *et al*. Clinical relevance of sentinel lymph nodes in the internal mammary chain in breast cancer patients. Eur J Nucl Med Mol Imaging 2005; 32(11): 1283-7.
79. Park C, Seid P, Morita E, Iwanaga K, Weinberg V, Quivey J, *et al*. Internal mammary sentinel lymph node mapping for invasive breast cancer: implications for staging and treatment. Breast J 2005; 11(1): 29-33.
80. Peley G, Sinkovics I, Toth J, Farkas E, Keresztes S, Koves I. Subareolar injection of radioactive colloid for sentinel lymph node identification in breast cancer patients. Am Surg 2004; 70(7): 625-9.
81. Povoski SP, Olsen JO, Young DC, Clarke J, Burak WE, Walker MJ, *et al*. Prospective randomized clinical trial comparing intradermal, intraparenchymal, and subareolar injection

routes for sentinel lymph node mapping and biopsy in breast cancer. Ann Surg Oncol 2006; 13(11): 1412-21.
82. Reitsamer R, Peintinger F, Rettenbacher L, Prokop E, Sedlmayer F. Subareolar subcutaneous injection of blue dye versus peritumoral injection of technetiumlabeled human albumin to identify sentinel lymph nodes in breast cancer patients. World J Surg 2003; 27(12): 1291-4.
83. Rink T, Heuser T, Fitz H, Schroth HJ, Weller E, Zippel HH. Results of a standardized protocol for sentinel node imaging in breast cancer with Tc-99m labeled nanocolloidal albumin. Nuklearmedizin 2001; 40(3): 80-5.
84. Hudack S, McMaster PD. The permeability of the wall of the lymphatic capillary. J Exp Med 1932; 56(2): 223-38.
85. Hudack SS, McMaster PD. The lymphatic participation in human cutaneous phenomena : a study of the minute lymphatics of the living skin. J Exp Med 1933; 57(5): 751-74.
86. Bronskill MJ. Radiation dose estimates for interstitial radiocolloid lymphoscintigraphy. Semin Nucl Med 1983; 13(1): 20-5.
87. Halsell JT, Smith JR, Bentlage CR, Park OK, Humphreys JW, Jr. Lymphatic drainage of the breast demonstrated by vital dye staining and radiography. Ann Surg 1965; 162(2): 221-6.
88. Farrus B, Vidal-Sicart S, Velasco M, Zanon G, Fernandez PL, Munoz M, *et al*. Incidence of internal mammary node metastases after a sentinel lymph node technique in breast cancer and its implication in the radiotherapy plan. Int J Radiat Oncol Biol Phys 2004; 60(3): 715-21.
89. Leidenius MH, Krogerus LA, Toivonen TS, Leppanen EA, von Smitten KA. The clinical value of parasternal sentinel node biopsy in breast cancer. Ann Surg Oncol 2006; 13(3): 321-6.
90. Madsen E, Gobardhan PD, Bongers V, Albregts M, Burgmans JPJ, Hooge P, *et al*. The impact on postsurgical treatment of sentinel lymph node biopsy of internal mammary lymph nodes in patients with breast cancer. Annals of Surgical Oncology 2007; 14(4): 1486-92.
91. Hindie E, Groheux D, Hennequin C, Zanotti-Fregonara P, Vercellino L, Berenger N, *et al*. Lymphoscintigraphy can select breast cancer patients for internal mammary chain radiotherapy. Int J Radiat Oncol Biol Phys 2012; 83(4): 1081-8.
92. Freedman GM, Fowble BL, Nicolaou N, Sigurdson ER, Torosian MH, Boraas MC, *et al*. Should internal mammary lymph nodes in breast cancer be a target for the radiation oncologist? Int J Radiat Oncol Biol Phys 2000; 46(4): 805-14.
93. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, *et al*. Effects of radiotherapy and ofdifferences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 366(9503): 2087-106.