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 affect 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 the identification rate. These observations can help in the selection of patients for IM sentinel node biopsy, which can affect their prognosis and treatment management.

Introduction

The pathological status of internal mammary (IM) nodes is integral to the tumor node metastasis (TNM) staging of breast cancer. 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\%\textsuperscript{2-5}. Using
Lymphoscintigraphy, extra-axillary drainage is seen up to one-third of the patients, most frequently to the IM chain. 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. 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 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) subcutaneous; 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 andug 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. 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. 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. 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: 0.3-9.6%) ($P = 0.01$), 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).

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

different from areolar at 2% (95% CI: 0.5-4.3%), subdermal at 3.2% (95% CI: 0.7-7.5%), and intradermal locations at 0.7% (95% 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 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 visualization for the superficial group was 1.7% (95% CI: 0.9-2.8%) and for the deep group 13.4% (95% CI: 11.4-15.5%) (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 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% (95% CI: 0.9-2.8%) and for the deep group 13.4% (95% CI: 11.4-15.5%) (P < 0.001). The ISIM rate was 0.2% (95% CI: 0.0-0.8%) for the superficial group and 1.3% (95% CI: 0.7-2%) for the deep group (P = 0.008).

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% (95% CI: 31.4-43%), was significantly different from all other single injection locations (P < 0.001). The around the tumor location at 12.8% (95% CI: 10.2-15.5%) was not significantly different from the intra tumoral location at 16.2% (95% CI: 12.4-20.5%) (P = 0.16), while these two locations were significantly different from areolar at 2% (95% CI: 0.5-4.3%) subdermal at 3.2% (95% CI: 0.7-7.5%), and intradermal locations at 0.7% (95% 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.
In this meta-analysis, the rate of IM identification was significantly higher in the deep injection group compared to the superficial injection group. Variation in lymphatic drainage has also been reported to be related to breast quadrant. These data indicate that tumors in differing locations and depth in the breast have different rates nodes. This meta-analysis demonstrated a significantly higher rate of visualization of 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. Moreover, unfiltered sulfur colloid did not demonstrate any difference in the 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.

**Discussion**

In this meta-analysis, the rate of IM identification was significantly higher in the deep injection group compared to the superficial injection group. Variation in lymphatic drainage has also been reported to be related to breast quadrant. 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. 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.

**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%).
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.8,9 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.7,8,11,24 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.20,28,38,44,40

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.3,4,9,12 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.53

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.2,3,9,12

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Conflict of interests

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