Published in final edited form as:

Cancer. 2012 December 15; 118(24): 6287–6296. doi:10.1002/cncr.27564.

Impact of Internal Mammary Lymph Node Drainage Identified by Preoperative Lymphoscintigraphy on Outcomes in Patients with Stage I to III Breast Cancer

Amanda L. Kong, MD, MS^{1,2}, Welela Tereffe, MD³, Kelly K. Hunt, MD¹, Min Yi, MD, PhD¹, Taewoo Kang, MD^{1,4}, Kimberly Weatherspoon¹, Elizabeth A. Mittendorf, MD¹, Isabelle Bedrosian, MD¹, Rosa F. Hwang, MD¹, Gildy V. Babiera, MD¹, Thomas A. Buchholz, MD², and Funda Meric-Bernstam, MD¹

¹Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas

²Department of Surgery, Medical College of Wisconsin, Milwaukee, Wisconsin (present affiliation)

³Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas

⁴Department of Surgery, Pusan National University Hospital, College of Surgery, Busan, Korea (present affiliation)

Abstract

BACKGROUND—Involvement of internal mammary (IM) lymph nodes is associated with a poor prognosis for patients with breast cancer. We examined the effect of drainage to IM nodes identified by lymphoscintigraphy on oncologic outcomes.

METHODS—A prospectively maintained breast cancer patient database at the University of Texas MD Anderson Cancer Center was used to identify patients with stage I to III breast cancer who underwent preoperative lymphoscintigraphy with peritumoral injection of colloid and intraoperative lymphatic mapping from 1996 to 2005. We reviewed the medical records of 1,772 patients who had drainage to any lymph node basin on lymphoscintigraphy but did not undergo IM nodal biopsy. Patients with IM drainage (with or without axillary drainage) were compared with patients without IM drainage. Local-regional recurrence (LRR), distant disease-free survival (DDFS), and overall survival (OS) were evaluated.

RESULTS—We identified IM drainage in 334 patients (18.8%). Patients with IM drainage were significantly younger, less likely to have upper outer quadrant tumors, and more likely to have smaller and medial tumors than patients without IM drainage. Rates of IM irradiation did not differ between the two groups. The median follow-up time was 7.4 years. On multivariate analysis, IM drainage was significantly associated with a worse DDFS (Hazard ratio, 1.6; 95% confidence interval, 1.03–2.6; $P = 0.04$) but not LRR or OS.

CONCLUSIONS—IM drainage on preoperative lymphoscintigraphy was found to be significantly associated with worse DDFS. Further study is needed to determine the role of lymphoscintigraphy in the personalization of breast cancer staging and therapy.

Corresponding author: Funda Meric-Bernstam, MD, Department of Surgical Oncology, Unit 1484, The University of Texas MD Anderson Cancer Center, 1400 Pressler St, Houston, TX 77030; Telephone: (713) 745-4453; Fax: (713) 745-4926; fmeric@mdanderson.org.

There are no relevant financial disclosures from any authors.

Keywords

Breast cancer; lymph nodes; internal mammary lymph nodes; lymphoscintigraphy

INTRODUCTION

The prognostic significance of metastatic disease in axillary lymph nodes has been well established in breast cancer patients.¹ Interest in metastases to the internal mammary (IM) nodal basin started with the extended radical mastectomy. Studies have demonstrated IM nodal involvement from 22% to 30% identified by resection of the IM nodal basin, or more recently, by sentinel node biopsy, with survival rates similar to those of patients with positive axillary nodes.^{2–4} Furthermore, involvement of both the axillary and the IM nodes has been shown to signify a worse prognosis than involvement of either basin alone.^{2, 3, 5} However, a randomized trial comparing radical mastectomy with extended radical mastectomy demonstrated no significant difference in patient survival at 30 years.⁶ Dissecting the IM nodes has therefore largely been abandoned because of the morbidity of the procedure and the lack of a demonstrated survival benefit.

Intraoperative lymphatic mapping and sentinel lymph node (SLN) dissection are commonly performed during mastectomy and lumpectomy for staging purposes and to determine whether nodal dissection is warranted. The axillary nodal basin is the most common site of lymphatic drainage from breast cancers, but some patients have drainage to extra-axillary sites, including the IM nodes. Tumors located in the medial aspect of the breast have been shown to preferentially drain to the IM nodal chain and have been shown to be associated with a worse prognosis than tumors located in the outer quadrants.^{7, 8}

Preoperative lymphoscintigraphy (LSG) aids in the identification of lymphatic drainage and can guide operative planning for breast cancer. LSG demonstrates drainage to the IM nodal basin in up to 45% of patients with breast cancer.⁹ Identification of IM drainage by LSG can have implications for treatment, recurrence, and ultimately survival.¹⁰ Several groups have used this information in conjunction with clinical factors (ie: age, tumor grade, etc...) to guide decisions regarding operative removal of the IM nodes as well as systemic and local-regional therapy.^{11–13} When drainage to the IM nodes is demonstrated, an IM SLN biopsy may help identify metastases, ultimately influencing staging and treatment.

We hypothesized that IM nodal drainage on preoperative LSG may identify breast cancer patients at risk of regional or systemic disease dissemination through additional drainage routes as well as patients who may have been understaged. The purpose of this study was to evaluate the association between IM drainage seen on preoperative LSG and oncologic outcomes in patients treated at a single institution before selective IM SLN mapping was incorporated into our practice.

MATERIALS AND METHODS

Patient Population

We used a prospectively maintained database at The University of Texas MD Anderson Cancer Center to identify 2,106 patients with invasive breast cancer (stage I to III) (American Joint Committee on Cancer Staging Manual 6th ed.¹⁴) who underwent preoperative LSG using peritumoral injection of the isotope followed by intraoperative lymphatic mapping between 1996 and 2005. Approximately 79% of patients underwent lymphoscintigraphy during this time period. The remainder did not undergo LSG due to scheduling issues or physician preference. Patients were excluded if they had stage IV

cancer, no invasive cancer, no nodal drainage on LSG, no pathologic data on primary tumor size, clinically positive nodes, or T4 tumors; if they underwent IM node biopsy or other IM node surgery; or if they were lost to follow-up within 1 year of surgery. The final cohort consisted of 1,772 patients. This retrospective study was approved by the MD Anderson Institutional Review Board.

The end points of the current study were local-regional recurrence (LRR), distant disease-free survival (DDFS), and overall survival (OS). Medical records were reviewed for demographics, clinicopathologic data, systemic therapy, and local-regional therapy, including nodal basins targeted for radiation therapy. Patients were categorized by whether any IM drainage was identified on LSG.

Preoperative LSG

All patients underwent LSG on the day before or day of surgery. Technetium 99m-labeled sulfur colloid was injected into the breast parenchyma around the primary tumor; 2.5 mCi was injected when LSG was performed on the day before surgery, and 0.5 mCi was used when LSG was done on the day of surgery. Thirty minutes to 1 hour after injection of the radiocolloid, images (anterior, posterior, and lateral) were taken by placing the patient under a scintillation camera for 2 to 6 minutes. Drainage was evidenced by the detection of tracer uptake in one or more nodal basins. If no drainage was visualized, additional images were obtained periodically for up to 5 hours after injection of the radiocolloid.

Statistical Methods

The clinical endpoints were LRR, DDFS, and OS calculated from the time of surgery to date of first local or regional recurrence (LRR), to date of first distant recurrence (DDFS) and date of death due to any cause (OS). Patients not experiencing those endpoints were censored at last follow-up.

We compared the two patient groups, those with IM drainage and those without IM drainage to identify differences in age, ethnicity, clinicopathologic characteristics, treatments, and outcomes. Differences in continuous variables were assessed using the two-sided *t*-test or Wilcoxon rank sum test. Differences in categorical variables were assessed using the chi-square or Fisher exact test. We performed univariate analyses to determine the influence of patient, tumor, and treatment factors of known or potential prognostic value on LRR, DDFS and OS determined using the Kaplan-Meier method. Factors with *p* value = 0.2 from the univariate analysis were included in multivariate Cox proportional hazards models to identify significant predictors of LRR, DDFS and OS. Statistical analyses were performed using Stata software (version 8.0; StataCorp, College Station, Texas), and *P* values less than .05 were considered statistically significant.

RESULTS

Patient and Tumor Characteristics

Of 1,772 patients who demonstrated any nodal drainage on LSG and had not undergone IM nodal biopsy, 334 (18.8%) showed IM drainage. Twenty-six patients (1.5%) showed IM drainage only, and 308 (17.4%) showed both IM and axillary drainage. Table 1 compares the patient and tumor characteristics of patients with and without IM drainage. Patients with IM drainage were significantly younger, were less likely to have upper outer quadrant tumors, were more likely to have medial tumors, and had a smaller median tumor size than patients without IM drainage. Tumor stage and axillary SLN status did not differ significantly between the two groups. In addition, there were no differences in tumor histology, estrogen receptor status, HER-2 status, or nuclear grade between the groups.

Local-Regional and Systemic Treatments

There were no differences in the rates of postoperative irradiation or of irradiation of the IM nodal basin between patients with IM drainage and patients without IM drainage (Table 2). Furthermore, among the patients who had axillary lymph node involvement, no differences were noted in the rates of IM field irradiation between patients with IM drainage and patients without IM drainage.

There were also no differences in the use of systemic therapy between the two patient groups. One hundred thirty-nine patients (41.6%) with IM drainage and 588 patients (40.9%) without IM drainage received chemotherapy ($P = 0.80$) (Table 2). Two hundred twenty-three (66.8%) of the 334 patients with IM drainage and 1,032 (71.8%) of 1,438 patients without IM drainage received endocrine therapy ($P = 0.07$).

Outcomes

Table 3 shows follow-up and recurrence data for patients with and without IM drainage. The median follow-up time for the entire cohort was 7.4 years (range 1–12.1). The median follow-up time was longer for those with IM drainage (7.7 years) than for those without IM drainage (7.3 years; $P = 0.001$).

Fifteen patients (4.5%) in the IM drainage group and 34 (2.4%) in the no IM drainage group had local recurrences ($P = 0.04$). There was no significant difference in 5-year regional recurrence rates between the two groups: 3.0% for IM drainage group and 1.6% for those without IM drainage ($P = 0.10$) and also no difference in 5 year distant recurrence rates between the two groups: 6.9% for the IM drainage group and 4.7% for those without IM drainage ($P = 0.10$).

When we analyzed factors associated with LRR, only younger age and negative estrogen receptor status were independent predictors on multivariate analysis (Table 4). We also analyzed factors associated with distant disease-free survival. On univariate analysis, younger age, lymphovascular invasion, grade 3 disease, T2–T3 tumors, negative estrogen receptor status, negative progesterone receptor status, and larger number of positive lymph nodes were negatively associated with DDFS (Table 5). However, on multivariate analysis, IM drainage was significantly associated with worse DDFS along with younger age, lymphovascular invasion, T2–T3 tumors, negative estrogen receptor status, and larger number of positive nodes. Negative predictors of OS on multivariate analysis were younger age, lymphovascular invasion, T2 tumors, negative estrogen receptor status, and larger number of positive lymph nodes (Table 6). IM drainage was not a predictor of OS.

DISCUSSION

Our study examined whether IM drainage revealed by preoperative LSG with peritumoral tracer injection is associated with poor outcomes in patients with stage I to III breast cancer. We found that patients with and without IM drainage received IM irradiation at similar rates, and that IM drainage itself was not a predictor of LRR or OS. However, we identified a worse DDFS in patients with IM drainage on preoperative LSG compared with those without IM drainage.

Several studies have demonstrated that metastasis to the IM lymph nodes portends a worse prognosis.^{2, 3, 15–17} Computed tomography and ultrasonography can be used to identify some IM nodal involvement but are not sensitive enough to detect low-volume IM nodal metastases. Investigators have demonstrated that treatment plans may be changed when IM nodal involvement is identified; however, treating the IM nodes in all patients would likely result in overtreatment.^{4, 13} In a study of breast cancer patients treated with extended radical

mastectomy, Yu et al found that more than 80% of patients in the axillary node–negative group received unnecessary IM radiation based on conventional indications.¹⁸ Therefore, an approach to identify patients at high risk of IM involvement and relapse is needed.

Noushi et al. utilized data from historical extended radical mastectomy series to project contemporary rates of IMN metastasis as well as SEER data to create a model to predict IM node status in patients.¹⁹ However, the model could not be validated. In addition, the authors noted that the two situations in which the model could be utilized are in 1) a center using high quality LSG which demonstrates high frequency of IMN mapping (33–37%) and 2) in a center where IMN mapping is less than ideal, all IMN that are mapped should have a biopsy. Applications of this model are limited in that most centers do not demonstrate such a high frequency of IMN mapping (Table 7) which may be due to technical aspects as almost all these series use technetium nanocolloid or sulfur colloid versus antimony labeled sulfur colloid which is utilized by this group. Biopsying of all IM nodes that are mapped is also impractical for many institutions.

Preoperative LSG can help identify patients who are at high risk of IM nodal metastases. Ideally, these patients could then be targeted for SLN biopsy of the IM nodes, which may provide more accurate staging of breast cancer. Patients with involvement of the IM nodes are one group who would benefit from further regional or systemic treatment, particularly those with no disease identified in the axillary nodes and no high-risk tumor features that would indicate the need for systemic therapy. Conversely, patients without metastases in the IM nodal basin could avoid the potential toxicity associated with IM irradiation. This indeed has been the practice at several institutions. However,^{11–13, 20, 21} However, even though biopsy remains the gold standard, there may still be a false negative rate secondary to shine through from medial tumors, multiple hot spots in multiple intercostals spaces and difficulty in retrieving the node.²²

A review of practices in multiple centers demonstrated that most surgeons do not perform IM SLN biopsy.²³ IM biopsy requires a skill set that not all surgeons may feel comfortable performing. It is also not without complications or morbidity. We have demonstrated that patients who drain to the IM nodal basin on LSG have worse DDFS.

Yao et al performed a similar study with 604 patients with stage I to III breast cancer who had undergone IM SLN mapping using peritumoral injection. They found that despite adjuvant treatment, the node-positive patients with IM drainage had a relatively poor prognosis (5-year OS rate, 71%) compared with the node-positive patients without IM drainage (5-year OS rate, 91%) and that IM nodal drainage predicted a nearly threefold increase in mortality risk in axillary node–positive patients.¹⁰ Utilizing that information in the context of other clinical factors (ie: positive axillary nodes, young age, etc...) may help guide adjuvant therapy decision-making.

These high risk patients may benefit from adjuvant therapy they may otherwise would not have received. In the era of personalized medicine with molecular tumor gene assays assisting in chemotherapy decisions, the role of IM radiation is unclear. It has been suggested that only certain subsets of patients may benefit from this therapy: those with early-stage disease who have primary drainage to the IM nodes on LSG, those with inner or central tumors and positive axillary lymph nodes, and those receiving postmastectomy radiation for advanced primary or nodal disease.²⁴ It has also been proposed that IM radiation should be considered only for those with pathologically proven IM nodal involvement with the goal of improving local-regional control.²⁵

Data from the NCIC-CTG MA.20 trial presented at the 2011 American Society of Clinical Oncology meeting may help to evaluate the role of IM irradiation on breast cancer

survival.²⁶ This trial evaluated the addition of regional nodal irradiation (RNI) to whole breast irradiation (WBI) following breast-conserving therapy which included segmental mastectomy and axillary lymph node dissection and adjuvant chemotherapy and/or endocrine therapy.²⁷ An important finding from the MA.20 study was that the addition of RNI lowered the absolute risk of a distant metastatic event from 13% down to 7.7% within 5 years of diagnosis.²⁶ This report suggests that 41% of distant metastatic events in the trial population could be prevented by RNI. These data provide evidence that very low volume disease in IM nodes that is untreated may have biologic relevance. A second randomized trial that may help to further determine the value of IM irradiation, is the European Organization for Research and Treatment of Cancer trial 22922, a phase III trial evaluating the impact of IM and medial supraclavicular nodal irradiation on long-term disease-free and overall survival in stage I to III breast cancer patients. One limitation of this study is that LSG was not used to select patients for IM radiotherapy which may dilute possible therapeutic effects. However, patients must have resected central or medial tumors which will likely capture most patients who potentially drain to the IMN. The trial has completed accrual. However, the results have not yet been published.

Our retrospective study has potential limitations, including those inherent in any retrospective study. It is a single-institution study; however, its cohort is almost twice as large as that of the Yao et al series which was the largest previously reported series. However, given that only 18.8% of patients had IM drainage and only a fifth of those patients would be expected to have IM involvement, our study is underpowered to address the impact of IM drainage on survival outcomes. This would need to be addressed in larger, multi-institutional series. The median follow-up time was 7.4 years, and a longer follow-up time is likely needed to make definitive conclusions about the effect of increased distant recurrences on OS. Breast cancer patients in our institution do not undergo routine surveillance imaging of the IM nodes after treatment; therefore, our results may underestimate rates of recurrence in IM nodes. Also, since our study goal was to determine the impact of LSG IM drainage on disease outcomes, we limited our study to patients who had LSG without IM SLN biopsy. Thus, we were not able to determine what portion of the 18.8% of patients with IM drainage in our series had IM involvement. Our study was also limited to patients who had undergone axillary SLN biopsy with clinically negative axillary nodes. Patients with clinically positive axillary nodes are more likely to have a greater disease burden in the IM nodes if there is IM drainage as well. However, the impact of IM drainage in that particular patient population was not the focus of our study.

In conclusion, we found a worse DDFS in patients with IM drainage on LSG compared with patients who did not have IM drainage on multivariate analysis. Evaluating IM drainage with preoperative LSG may help guide therapy by identifying patients at high risk of relapse. Further study is needed to determine whether LSG and IM nodal mapping can be used to improve staging and personalize local-regional therapy.

Acknowledgments

Funding Sources: The University of Texas MD Anderson Cancer Center is supported in part by a cancer center support grant from the National Institutes of Health (CA16672).

References

1. Fitzgibbons PL, Page DL, Weaver D, et al. Prognostic factors in breast cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med. Jul; 2000 124(7):966–978. [PubMed: 10888772]
2. Donegan WL. The influence of untreated internal mammary metastases upon the course of mammary cancer. Cancer. Feb; 1977 39(2):533–538. [PubMed: 837336]

3. Cody HS 3rd, Urban JA. Internal mammary node status: a major prognosticator in axillary node-negative breast cancer. *Ann Surg Oncol.* Jan; 1995 2(1):32–37. [PubMed: 7834452]
4. Madsen E, Gobardhan P, Bongers V, et al. The impact on post-surgical treatment of sentinel lymph node biopsy of internal mammary lymph nodes in patients with breast cancer. *Ann Surg Oncol.* Apr; 2007 14(4):1486–1492. [PubMed: 17253106]
5. Klauber-DeMore N, Bevilacqua JL, Van Zee KJ, Borgen P, Cody HS 3rd. Comprehensive review of the management of internal mammary lymph node metastases in breast cancer. *J Am Coll Surg.* Nov; 2001 193(5):547–555. [PubMed: 11708513]
6. Veronesi U, Marubini E, Mariani L, Valagussa P, Zucali R. The dissection of internal mammary nodes does not improve the survival of breast cancer patients. 30-year results of a randomised trial. *Eur J Cancer.* Sep; 1999 35(9):1320–1325. [PubMed: 10658521]
7. Shahar KH, Buchholz TA, Delpassand E, et al. Lower and central tumor location correlates with lymphoscintigraphy drainage to the internal mammary lymph nodes in breast carcinoma. *Cancer.* Apr 1; 2005 103(7):1323–1329. [PubMed: 15726547]
8. Colleoni M, Zahrieh D, Gelber RD, et al. Site of primary tumor has a prognostic role in operable breast cancer: the international breast cancer study group experience. *J Clin Oncol.* Mar 1; 2005 23(7):1390–1400. [PubMed: 15735115]
9. Uren RF, Howman-Giles R, Renwick SB, Gillett D. Lymphatic mapping of the breast: locating the sentinel lymph nodes. *World J Surg.* Jun; 2001 25(6):789–793. [PubMed: 11376417]
10. Yao MS, Kurland BF, Smith AH, et al. Internal mammary nodal chain drainage is a prognostic indicator in axillary node-positive breast cancer. *Ann Surg Oncol.* Oct; 2007 14(10):2985–2993. [PubMed: 17564747]
11. Galimberti V, Veronesi P, Arnone P, et al. Stage migration after biopsy of internal mammary chain lymph nodes in breast cancer patients. *Ann Surg Oncol.* Nov; 2002 9(9):924–928. [PubMed: 12417517]
12. Tanis PJ, Nieweg OE, Valdes Olmos RA, et al. Impact of non-axillary sentinel node biopsy on staging and treatment of breast cancer patients. *Br J Cancer.* Sep 23; 2002 87(7):705–710. [PubMed: 12232750]
13. 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.* Oct; 2003 10(8):935–941. [PubMed: 14527914]
14. Greene FL. American Joint Committee on Cancer., American Cancer Society. *AJCC cancer staging manual.* 6. New York: Springer-Verlag; 2002.
15. Veronesi U, Cascinelli N, Greco M, et al. Prognosis of breast cancer patients after mastectomy and dissection of internal mammary nodes. *Ann Surg.* Dec; 1985 202(6):702–707. [PubMed: 3000303]
16. Urban JA, Marjani MA. Significance of internal mammary lymph node metastases in breast cancer. *Am J Roentgenol Radium Ther Nucl Med.* Jan; 1971 111(1):130–136.
17. Sugg SL, Ferguson DJ, Posner MC, Heimann R. Should internal mammary nodes be sampled in the sentinel lymph node era? *Ann Surg Oncol.* Apr; 2000 7(3):188–192. [PubMed: 10791848]
18. Yu J, Li G, Li J, Wang Y. The pattern of lymphatic metastasis of breast cancer and its influence on the delineation of radiation fields. *Int J Radiat Oncol Biol Phys.* Mar 1; 2005 61(3):874–878. [PubMed: 15708269]
19. Noushi F, Spillane AJ, Uren RF, Gebiski V. Internal mammary node metastasis in breast cancer: predictive models to determine status & management algorithms. *Eur J Surg Oncol.* Jan; 2010 36(1):16–22. [PubMed: 19846271]
20. Mansel RE, Goyal A, Newcombe RG. Internal mammary node drainage and its role in sentinel lymph node biopsy: the initial ALMANAC experience. *Clin Breast Cancer.* Oct; 2004 5(4):279–284. discussion 285–276. [PubMed: 15507173]
21. Paredes P, Vidal-Sicart S, Zanon G, et al. Clinical relevance of sentinel lymph nodes in the internal mammary chain in breast cancer patients. *Eur J Nucl Med Mol Imaging.* Nov; 2005 32(11):1283–1287. [PubMed: 16007422]
22. Spillane AJ, Noushi F, Cooper RA, Gebiski V, Uren RF. High-resolution lymphoscintigraphy is essential for recognition of the significance of internal mammary nodes in breast cancer. *Ann Oncol.* Jun; 2009 20(6):977–984. [PubMed: 19153113]

23. Chagpar AB, Kehdy F, Scoggins CR, et al. Effect of lymphoscintigraphy drainage patterns on sentinel lymph node biopsy in patients with breast cancer. *Am J Surg.* Oct; 2005 190(4):557–562. [PubMed: 16164919]
24. Buchholz TA. Internal mammary lymph nodes: to treat or not to treat. *Int J Radiat Oncol Biol Phys.* Mar 1; 2000 46(4):801–803. [PubMed: 10704999]
25. Freedman GM, Fowble BL, Nicolaou N, et al. Should internal mammary lymph nodes in breast cancer be a target for the radiation oncologist? *Int J Radiat Oncol Biol Phys.* Mar 1; 2000 46(4): 805–814. [PubMed: 10705000]
26. Whelan T, Olivotto I, Ackerman I, et al. NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer. *J Clin Oncol.* 2011; 29(18_suppl):LBA 1003.
27. Olivotto IA, Chua B, Elliott EA, et al. A clinical trial of breast radiation therapy versus breast plus regional radiation therapy in early-stage breast cancer: the MA20 trial. *Clin Breast Cancer.* Dec; 2003 4(5):361–363. [PubMed: 14715112]
28. Johnson N, Soot L, Nelson J, et al. Sentinel node biopsy and internal mammary lymphatic mapping in breast cancer. *Am J Surg.* May; 2000 179(5):386–388. [PubMed: 10930486]
29. Noguchi M, Tsugawa K, Miwa K. Internal mammary chain sentinel lymph node identification in breast cancer. *J Surg Oncol.* Feb; 2000 73(2):75–80. [PubMed: 10694642]
30. Dupont E, Cox CE, Nguyen K, et al. Utility of internal mammary lymph node removal when noted by intraoperative gamma probe detection. *Ann Surg Oncol.* Dec; 2001 8(10):833–836. [PubMed: 11776499]
31. van der Ent FW, Kengen RA, van der Pol HA, Povel JA, Stroeken HJ, Hoofwijk AG. Halsted revisited: internal mammary sentinel lymph node biopsy in breast cancer. *Ann Surg.* Jul; 2001 234(1):79–84. [PubMed: 11420486]
32. Farrus B, Vidal-Sicart S, Velasco 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.* Nov 1; 2004 60(3):715–721. [PubMed: 15465187]
33. Carcoforo P, Sortini D, Feggi L, 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.* Oct; 2006 13(10):1338–1343. [PubMed: 16952022]
34. Veronesi U, Arnone P, Veronesi P, et al. The value of radiotherapy on metastatic internal mammary nodes in breast cancer. Results on a large series. *Ann Oncol.* May 7; 2008 19(9):1553–1560. [PubMed: 18467318]
35. Avisar E, Molina MA, Scarlata M, Moffat FL. Internal mammary sentinel node biopsy for breast cancer. *Am J Surg.* Oct; 2008 196(4):490–494. [PubMed: 18723148]
36. Coombs NJ, Boyages J, French JR, Ung OA. Internal mammary sentinel nodes: ignore, irradiate or operate? *Eur J Cancer.* Mar; 2009 45(5):789–794. [PubMed: 19121579]
37. 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.* Mar; 2009 35(3):252–257. [PubMed: 18684584]
38. Domenech-Villardell A, Bajen MT, Benitez AM, et al. Removal of the internal mammary sentinel node in breast cancer. *Nucl Med Commun.* Dec; 2009 30(12):962–970. [PubMed: 19696690]
39. van Esser S, Madsen EV, van Dalen T, et al. Axillary staging in breast cancer patients with exclusive lymphoscintigraphic drainage to the internal mammary chain. *World J Surg.* Jan; 2011 35(1):159–164. [PubMed: 20936283]

Table 1

Patient and Tumor Characteristics for Patients with IM Drainage (IM Only or IM and Axillary Drainage) and Without IM Drainage on Preoperative Lymphoscintigraphy^a

Characteristic	Total n = 1772	IM Drainage n = 334	No IM Drainage n = 1438	P Value
Age, y				<0.0001
Mean	56.1	53	56.8	
Median	56	52	56	
Range	23–88	26–83	23–88	
Tumor location				0.001
UOQ	688 (38.8)	102 (30.5)	586 (40.8)	
Other quadrant	1084 (61.2)	232 (69.5)	852 (59.2)	
Tumor location				0.002
Medial	440 (24.8)	105 (31.4)	335 (23.3)	
Lateral or central	1332 (75.2)	229 (68.6)	1103 (76.7)	
Tumor stage				0.1
T1	1353 (76.4)	268 (80.2)	1085 (75.5)	
T2	383 (21.6)	62 (18.6)	321 (22.3)	
T3	36 (2.0)	4 (1.2)	32 (2.2)	
Histology				0.1
IDC	1354 (76.4)	268 (80.2)	1086 (75.5)	
ILC	126 (7.1)	15 (4.5)	111 (7.7)	
IDC and ILC	153 (8.6)	24 (7.2)	129 (9.0)	
Other	139 (7.8)	27 (8.1)	112 (7.8)	
Number of axillary SLNs identified				0.9 ^b
Mean	2.8	2.8	2.8	
Median	2	2.5	2	
Range	0–10	0–9	0–10	
Final tumor size, cm				0.02 ^b
Mean	1.6	1.5	1.6	
Median	1.4	1.2	1.5	
Range	0.005–13	0.05–7	0.005–13	
Positive SLNs				0.4 ^c
Yes	405 (23.1)	69 (21.2)	336 (23.5)	
No	1348 (76.9)	256 (78.8)	1092 (76.5)	
Not identified	19	9	10	
ER status				0.5 ^c
Positive	1336 (75.4)	246 (73.6)	1090 (75.8)	
Negative	342 (19.3)	69 (20.7)	273 (19.0)	
Unknown	94 (5.3)	19 (5.7)	75 (5.2)	

Characteristic	Total n = 1772	IM Drainage n = 334	No IM Drainage n = 1438	P Value
PR status				0.03 ^c
Positive	1096 (61.9)	190 (56.9)	906 (63.0)	
Negative	552 (31.2)	120 (35.9)	432 (30.0)	
Unknown	124 (7.0)	24 (7.2)	100 (7.0)	
HER-2 status				0.1 ^c
Positive	236 (13.3)	53 (15.9)	183 (12.7)	
Negative	1300 (73.4)	238 (71.3)	1062 (73.8)	
Unknown	236 (13.3)	43 (12.8)	193 (13.4)	
Nuclear grade				0.4 ^c
1	252 (14.2)	50 (15.0)	202 (14.1)	
2	941 (53.1)	167 (50.0)	774 (54.1)	
3	571 (32.2)	117 (35.0)	454 (31.8)	
Unknown	8 (0.5)	0 (0)	8 (0.06)	

IM indicates internal mammary; UOQ, upper outer quadrant; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; SLN, sentinel lymph node; ER, estrogen receptor; PR, progesterone receptor.

^aData are number of patients (%) unless otherwise specified.

^bWilcoxon rank sum test.

^cP value calculated after excluding "Unknown" or "Not identified" category.

Table 2Adjuvant Treatments by Drainage Pattern^a

Characteristic	Total n =1772	IM Drainage n = 334	No IM Drainage n = 1438	P Value
Chemotherapy				0.8
Yes	727 (41.0)	139 (41.6)	588 (40.9)	
No	1045 (59.0)	195 (58.4)	850 (59.1)	
Endocrine therapy				.07
Yes	1255 (70.8)	223 (66.8)	1032 (71.8)	
No	517 (29.2)	111 (33.2)	406 (28.2)	
XRT				0.2
Yes	1167 (65.9)	210 (62.9)	957 (66.6)	
No	605 (34.1)	124 (37.1)	481 (33.4)	
IM XRT				0.9 ^b
Yes	69 (3.9)	13 (3.9)	56 (3.9)	
No	1387 (78.3)	255 (76.3)	1132 (78.7)	
Unknown	315 (17.8)	66 (19.8)	250 (17.4)	
Patients with positive SLNs	n = 405	n = 69	n = 336	
IM XRT				0.5 ^b
Yes	50 (12.4)	10 (14.5)	40 (11.9)	
No	288 (71.1)	46 (66.7)	242 (72.0)	
Unknown	67 (16.5)	13 (18.8)	54 (16.1)	

IM indicates internal mammary; SLN, sentinel lymph node; XRT, external beam radiation therapy.

^aData are number of patients (%).

^bP value calculated after excluding "unknown" category.

Table 3Follow-Up and Recurrence By Drainage Pattern^a

Outcome	Total n = 1772	IM Drainage n = 334	No IM Drainage n = 1438	P Value
Follow-up time, y				0.001
Mean	7.4	8.0	7.3	
Median	7.4	7.7	7.3	
Range	1–12.1	1–12	1–12.1	
Systemic recurrence				0.10 ^b
Yes	90 (5.1)	23 (6.9)	67 (4.7)	
No	1682 (94.9)	311 (93.1)	1371 (95.3)	
Local recurrence				0.04 ^b
Yes	49 (2.8)	15 (4.5)	34 (2.4)	
No	1723 (97.2)	319 (95.5)	1404 (97.6)	
Regional recurrence				0.10 ^b
Yes	33 (1.9)	10 (3.0)	23 (1.6)	
No	1739 (98.1)	324 (97.0)	1415 (98.4)	

IM indicates internal mammary; XRT, external beam radiation therapy.

^aData are number of patients (%) unless otherwise indicated.^bFisher exact test.

Table 4

Univariate and Multivariate Cox Proportional Hazards Models Predicting Local-Regional Recurrence

Characteristics	Univariate Analysis		Multivariate Analysis		
	HR	P Value	HR	P Value	95% CI
Age					
< 50 y	Referent		Referent		
50 y	0.4	<0.0001	0.5	0.004	0.3–0.8
IM drainage	1.6	0.08	1.3	0.2	0.8–2.2
UOQ tumor location	0.9	0.8			
Medial tumor location	1.4	0.2	1.5	0.2	0.8–2.9
LVI	1.3	0.4			
Nuclear grade					
1	Referent				
2	0.8	0.6	0.6	0.2	0.2–1.3
3	1.8	0.1	0.7	0.4	0.3–1.7
Tumor stage					
T1	Referent				
T2	1.6	0.08	1.4	0.2	0.8–2.5
T3	2.3	0.2	2.5	0.2	0.7–9.5
Negative ER status	3.4	<0.0001	3.2	<0.0001	1.9–5.1
Negative PR status	2.0	0.005	1.3	0.4	0.7–2.2
Negative HER-2 status	0.8	0.5			
Tumor histology					
IDC	Referent				
ILC	0.5	.2	0.6	0.4	0.2–2.1
IDC and ILC	0.6	.3	0.9	0.8	0.3–2.3
Other	0.3	.1	0.3	0.2	0.1–1.5
Number of positive LNs ^a	1.0	.9			

HR indicates hazards ratio; CI, confidence interval; IM, internal mammary; UOQ, upper outer quadrant; LVI, lymphovascular invasion; ER, estrogen receptor; PR, progesterone receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LN, lymph node.

^aAs a continuous variable.

Table 5

Univariate and Multivariate Cox Proportional Hazards Models Predicting Distant Disease-Free Survival

Characteristic	Univariate Analysis		Multivariate Analysis	
	HR	P Value	HR	95% CI
Age				
< 50 y	Referent		Referent	
50 y	0.4	<0.0001	0.6	0.4–0.9
IM drainage	1.5	0.07	1.6	1.03–2.6
UOQ tumor location	1.1	0.8		
Medial tumor location	1.3	0.2	1.5	0.9–2.5
LVI	2.7	<0.0001	2.0	1.2–3.4
Nuclear grade				
1	Referent			
2	1.3	0.6	1.1	0.4–2.7
3	3.8	0.002	2.0	0.8–5.3
Tumor stage				
T1	Referent		Referent	
T2	3.4	<0.0001	2.6	<0.0001
T3	8.3	<0.0001	4.5	0.001
Negative ER status	3.4	<0.0001	3.2	<0.0001
Negative PR status	1.6	0.03	0.9	0.7
Negative HER-2 status	1.1	0.7		
Tumor histology				
IDC	Referent			
ILC	1.1	0.7		
IDC and ILC	0.69	0.4		
Other	0.8	0.7		
Number of positive LNs ^a	1.1	<0.0001	1.6	0.006
				1.1–2.2

HR indicates hazards ratio; CI, confidence interval; IM, internal mammary; UOQ, upper outer quadrant; LVI, lymphovascular invasion; ER, estrogen receptor; PR, progesterone receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LN, lymph node.

^aAs a continuous variable.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 6

Univariate and Multivariate Cox Proportional Hazards Models Predicting Overall Survival

Characteristic	Univariate Analysis		Multivariate Analysis	
	HR	P Value	HR	95% CI
Age				
< 50 y	Referent		Referent	
50 y	0.4	<0.0001	0.6	0.4–0.9
IM drainage	0.9	0.5		
UOQ tumor location	1.0	0.997		
Medial tumor location	1.1	0.7		
LVI	1.5	0.03	1.6	1.04–2.3
Nuclear grade				
1	Referent			
2	0.9	0.6	0.8	0.5–1.4
3	1.7	0.04	1.2	0.7–2.2
Tumor stage				
T1	Referent		Referent	
T2	1.6	0.007	1.5	1.04–2.1
T3	2.3	0.046	2.2	0.9–5.4
Negative ER status	2.4	<0.0001	2.8	2.0–3.9
Negative PR status	1.3	0.06	0.8	0.5–1.1
Negative HER-2 status	0.9	0.5		
Tumor histology				
IDC	Referent			
ILC	0.9	0.6		
IDC and ILC	0.8	0.5		
Other	1.3	0.4		
Number of positive LNs ^a	1.1	0.003	1.3	1.02–1.7

HR indicates hazards ratio; CI, confidence interval; IM, internal mammary; UOQ, upper outer quadrant; LVI, lymphovascular invasion; ER, estrogen receptor; PR, progesterone receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LN, lymph node.

^aAs a continuous variable.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 7

Incidence of IM Drainage and Pathologically Confirmed IM Nodal Metastases in Published Series of Breast Cancer Patients

First Author	Year	IM Drainage on LSG	IMN+	IMN+/ALN-
Johnson ²⁸	2000	12.5% (10/80)	30% (3/10)	0%
Noguchi ²⁹	2000	12.2% (5/41)	10.5% (2/19)	N/A
Dupont ³⁰	2001	N/A	16.7% (5/30)	10% (3/30)
van der Ent ³¹	2001	25.4% (65/256)	26.8% (11/41)	7.3% (3/41)
Uren ⁹	2001	45% (71/159) ^{a,b}		
Galimberti ¹¹	2002	N/A	8.8% (14/160) ^c	2.5% (4/160)
Tanis ¹²	2002	19.1% (105/549) ^d	18.9% (17/90)	8.9% (8/90)
Estourgie ¹³	2003	21.7% (150/691)	16.9% (22/130)	6.9% (9/130)
Farrus ³²	2004	13.8% (31/225)	14.3% (2/14)	0%
Mansel ²⁰	2004	8.8% (62/707)	12.9% (4/31)	6.5% (2/31)
Paredes ²¹	2005	14.1% (55/391)	12.5% (4/32)	0%
Carcoforo ³³	2006	12.8% (95/741)	15.4% (10/65)	4.6% (3/65)
Madsen ⁴	2007	21.7% (109/502)	23.5% (20/85)	4.7% (4/85)
Veronesi ³⁴	2008	40.8% (254/623) ^e	10.3% (68/663)	2.6% (17/663)
Avisar ³⁵	2008	N/A	25.0% (7/28)	7.1% (2/28)
Coombs ³⁶	2009	18.0% (88/490) ^b	22.2% (20/90)	13.3% (12/90)
Heuts ³⁷	2009	19.4% (196/1008)	22% (31/139)	29% (9/31)
Domenech-Vilardell ³⁸	2009	9.0% (82/914)	13.6% (6/44)	9.1% (4/44)
Van Esser ³⁹	2011	19.0% (426/2203)	25.0% (4/16) ^f	6.2% (1/16)

IM indicates internal mammary; LSG, lymphoscintigraphy; IMN, internal mammary lymph node; +, positive for metastasis; ALN, axillary lymph node; -, negative for metastasis; N/A, not available.

^a IM node biopsy was not performed in this series

^b Series used antimony labeled sulfur colloid, rest of series used nanocolloid or sulfur colloid

^c IM sentinel lymph node biopsy was performed only in patients with medial tumor or who demonstrated IM drainage on LSG

^d One patient had drainage to the contralateral IM chain.

^e Patients has mostly inner quadrant tumors (520/663)

^f IM sentinel lymph node biopsy was performed only in patients who demonstrated IM chain drainage only (25/2203) and was successful in 16.