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ORIGINAL ARTICLE – BREAST ONCOLOGY

Additional Tracer Injection to Improve the Technical Success Rate of Lymphoscintigraphy for Sentinel Node Biopsy in Breast Cancer

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ABSTRACT

Background. Sentinel node (SN) biopsy has become the standard of care in the treatment of breast cancer. The aim of this study is to determine the value of additional tracer injection to increase the technical success rate of the SN procedure and to identify factors that influence the ability to visualize hotspots.

Methods. From February 1997 to August 2007, 1,208 clinically node-negative breast cancer patients underwent lymphatic mapping for SN biopsy. The technique involved the injection of 370 MBq (10 mCi) Tc-99 m-nanocolloid peritumorally. In case of insufficient or absent visualization of hotspots 37 MBq (1 mCi) of additional tracer was given intracutaneously above the tumor.

Results. In 93 patients (7.7%) visualization of hotspots on initial lymphoscintigraphy was insufficient (41 patients) or absent (52 patients). The first 14 patients did not receive additional tracer injection. In five patients, additional tracer did not result in successful lymphoscintigraphy, which is correlated with massive nodal tumor infiltration. In 33 patients with negative initial lymphoscintigraphy, additional tracer injection resulted in secondary SN visualization. In 41 patients with faint hotspots on initial lymphoscintigraphy, additional tracer injection, by increasing nodal uptake, simplified accurate SN biopsy. Decreased radiotracer uptake in this group was associated with older age and high body mass index (BMI).

Conclusions. Additional tracer injection following initial scan failure increases the success rate of lymphoscintigraphy during lymphatic mapping in breast cancer, without compromising accuracy. If additional tracer injection does not result in secondary SN visualization, gross nodal tumor involvement is often present and axillary lymph node dissection (ALND) is mandatory.

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Since the introduction of the sentinel node (SN) procedure in breast cancer, many validation studies have confirmed the accuracy of the SN biopsy in predicting axillary node status.[1–6] As compared with axillary lymph node dissection (ALND), SN biopsy causes less morbidity and provides the same staging information. As a consequence, ALND is nowadays abandoned in case of a negative SN biopsy, thereby avoiding unnecessary morbidity and costs associated with ALND.

However, sometimes the lymphatic mapping procedure fails because of insufficient or absent radioactive tracer uptake in the lymph nodes. Because a negative preoperative lymphoscintigraphy is predictive for failure of intraoperative SN identification, faint or nonvisualization of hotspots on lymphoscintigraphy (initial scan failure) frequently results in the need to perform ALND.[7]

After having experienced 14 patients with a negative preoperative lymphoscintigraphy in the first 3 years of our study, we started to use additional radiocolloid tracer injections as of May 2000, to avoid technical failure of the lymphatic mapping procedure.

The aim of this study is to determine the value of additional tracer injection to increase the technical success rate of the sentinel node procedure in case of a vague or negative lymphoscintigraphy and to identify factors that influence nonvisualization of hotspots.

PATIENTS AND METHODS

From April 1997 to August 2007, after having received approval of the Local Ethical Committee, and after informed consent, a total of 1,208 consecutive patients with clinically node-negative operable primary breast cancer were included in a prospective study on SN biopsy. In phase I of this study (137 patients) SN biopsy was followed by completion axillary lymph node dissection in all cases. In phase II, after validation of the SN technique in our institute, completion axillary lymph node dissection was performed only in cases of tumor-positive axillary SN or unsuccessful SN procedure. From this ongoing prospective study we analyzed all consecutive patients who showed inadequate or absent visualization of hotspots on the initial lymphoscintigraphic images (Figs. 1–3).

Our technique of SN biopsy has been described in detail elsewhere.[2] The lymphatic mapping procedure consists of 370 MBq (10 mCi) TC-99 m-nanocolloid injected peritumorally or in the breast parenchyma surrounding the cavity of a previous excisional biopsy. All patients underwent preoperative lymphoscintigraphy following a mean interval of 16 h (range 12–18 h). In case of initial scan failure, additional radiocolloid tracer injections of 37 MBq (1 mCi) Tc-99 m-nanocolloid intracutaneously above the tumor were used as of May 2000, in order to increase the technical success rate of lymphoscintigraphy by obtaining secondary SN visualization. A second lymphoscintigraphy was performed 10–15 min after the additional tracer injection was given.

In relation to the mapping procedure, radiation exposure guidelines and doses were considered for both patients and personnel and were found to be well within legal safety limits, as published previously.[2]

In 2002 preoperative ultrasonography of the axilla was introduced in our hospital and became standard procedure in combination with fine-needle aspiration (FNA) cytology in case of clinically or radiologically suspicious axillary lymph nodes. Thus, patients treated before 2002 did not receive routine ultrasound investigation of the axilla.

During surgery, all axillary and nonaxillary SNs were pursued, as visualized by lymphoscintigraphy. Intraoperative identification of the SNs was based both on blue dye mapping and gamma probe detection. In all cases of a failed SN procedure, whether based on secondary scan failure or based on intraoperative SN identification failure, ALND was performed, which involved at least removal of all level I and II lymph nodes.

Histopathologic examination of the SN consisted of routine serial sectioning with hematoxylin and eosin (H&E) staining, followed by immunohistochemical (IHC) staining, whenever routine H&E staining did not reveal metastases.

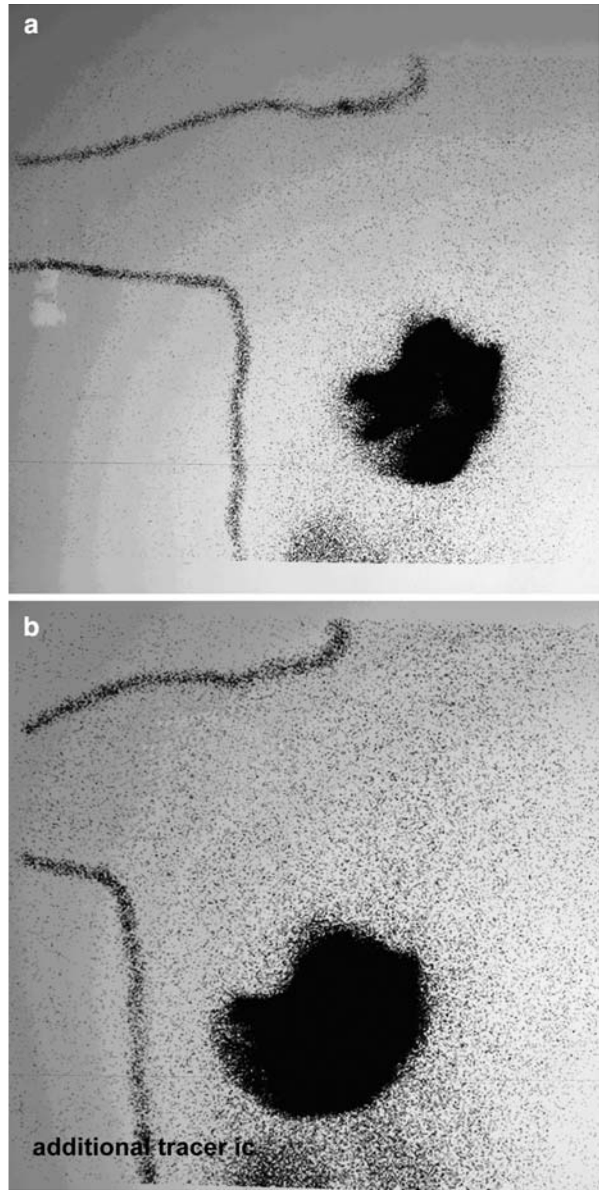

FIG. 1 Lymphoscintigraphy of patient with initial scan failure (**a**) and secondary scan failure after additional tracer injection (**b**)

Depending on the type of variable, chi-squared test or *t*-test was used to compare the characteristics of patients with successful lymphoscintigraphy and with initial scan failure.

RESULTS

In all, 1,208 consecutive patients with clinically node-negative breast cancer were included in this study. Patient and tumor characteristics are listed in Table 1.

Initial Scan Failure

In 93 patients, the results of preoperative lymphoscintigraphy were classified as initial scan failure: in 52

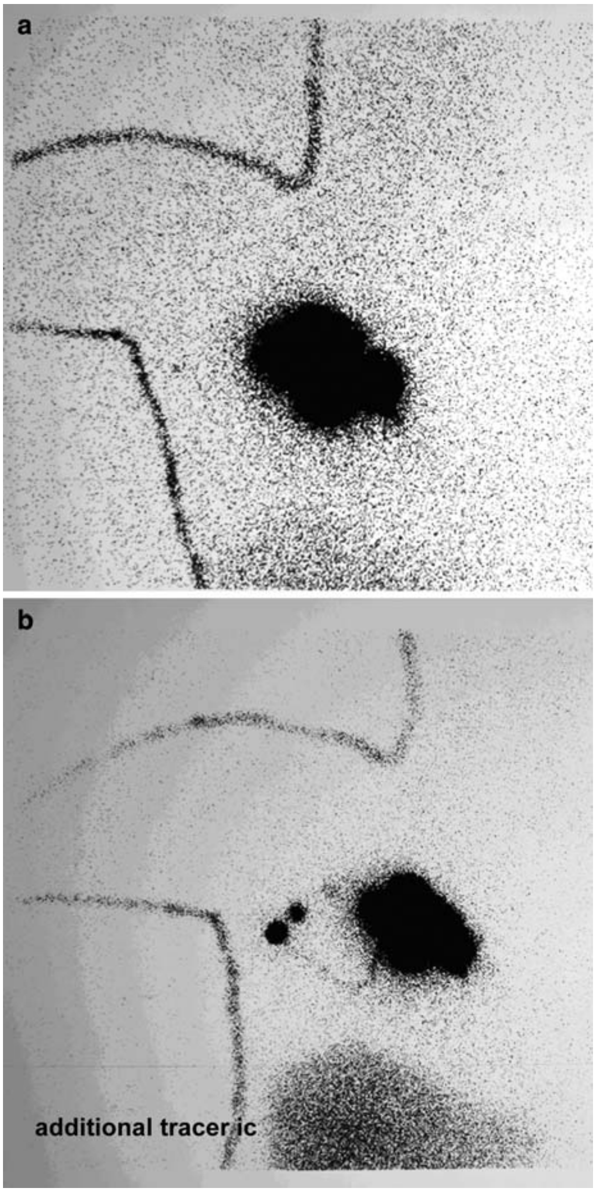

FIG. 2 Lymphoscintigraphy of patient with initial scan failure (**a**), but secondary SN visualization after additional tracer injection (**b**)

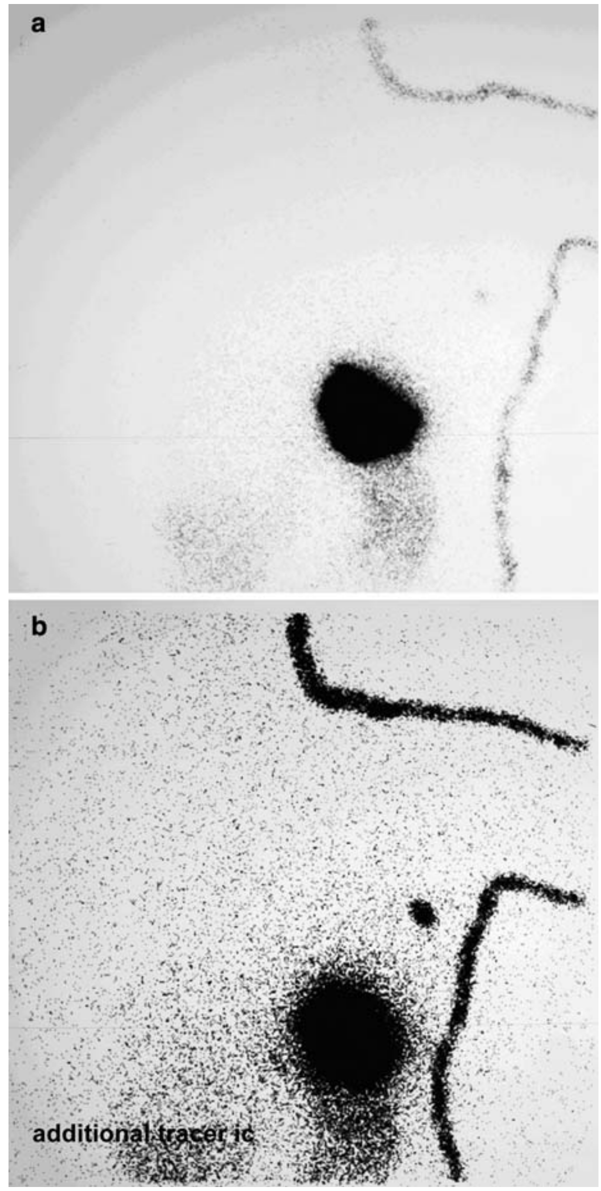

FIG. 3 Lymphoscintigraphy of patient with faint hotspot (**a**), but clear hotspot after additional tracer injection (**b**)

patients, because lymphoscintigraphy showed no axillary hotspots at all (negative lymphoscintigraphy), and in 41 patients because the initial SN visualization was considered inadequate (i.e., too faint to allow successful intraoperative SN retrieval). The mean age of these 93 patients was 65.8 years, compared with 58.5 years for the remaining group of 1,115 patients with clear hotspots on initial lymphoscintigraphy ($p < 0.0001$).

Within the first 3 years of the study 14 patients (group A, Table 2) with negative initial lymphoscintigraphy did not receive additional tracer injection and consequently ALND was performed in all cases. Of these 14 patients, 10 were found to have positive lymph nodes, with 5 of them having more than ten involved nodes. The remaining four patients had a negative SN procedure, using the blue dye technique, which was confirmed by completion ALND. No axillary recurrences were seen in these four patients within a median follow-up of 80 months.

As of May 2000, in case of initial scan failure, an additional tracer injection of 1 mCi Tc-99 m-nanocolloid intracutaneously was routinely used.

Secondary Scan Failure

In five patients (group B, Table 2) with initial scan failure, following additional tracer injection, repeated lymphoscintigraphy still did not show hotspots (Fig. 1a, b). Mean age of these patients was 66.2 years. Successful SN harvesting was possible in only one patient, because a (tumor-positive) palpable lymph node was found intraoperatively.

Axillary dissection was done in all five patients and showed a tumor-positive axilla in four (80%), of whom three patients showed massive tumor infiltration of almost all axillary lymph nodes. The only node-negative patient in this subgroup had no axillary recurrence during a follow-up period of 49 months.

Secondary SN Visualization

In 33 patients (group C, Table 2) with initial scan failure, we noted secondary SN visualization on repeated lymphoscintigraphy as a direct result of additional tracer injection (Fig. 2a, b). In these patients mean age was 64.7 years. Secondary lymphoscintigraphy clearly showed one or more axillary hotspots, which subsequently could be harvested in all cases, showing a positive SN in 17 patients (52%), all of whom underwent ALND. Massive nodal tumor burden, with ten or more tumor-positive nodes, was

TABLE 1 Comparison of characteristics of patients (N = 1208) with successful lymphoscintigraphy and with initial scan failure

Characteristic	Successful lymphoscintigraphy (n = 1,115)		Initial scan failure (n = 93)		p-value
	N	%	n	%	
Age (years)					<0.0001
≤50	346	31	10	11	
51–70	544	49	52	56	
>70	225	20	31	33	
Tumor localization					0.23
Lateral	615	55	43	46	
Medial	395	36	40	43	
Central	105	9	10	11	
Tumor size					<0.0001
DCIS/Paget	37	3	1	1	
T1	653	59	46	49	
T2	398	36	34	37	
T3	27	2	12	13	
Number of positive lymph nodes					<0.0001
0	676	61	46	49	
1–3	351	31	24	26	
>3	88	8	23	25	
Tumor grade					0.43
Good	286	26	29	31	
Moderate	478	43	39	42	
Poor	351	31	25	27	
Surgery					0.84
Core biopsy	932	84	77	83	
Previous excisional biopsy	183	16	16	17	
Estrogen receptor status					0.80
Negative	215	21	19	22	
Positive	823	79	68	78	
Missing values	77		6		
Progesterone receptor					0.14
Negative	367	35	24	28	
Positive	670	65	63	72	
Missing values	78		6		
IM hotspots on lymphoscintigraphy	236	21	5	5	<0.0001
BMI	100[a]	25.5[b]	93	29.0[b]	<0.0001

DCIS ductal carcinoma in situ

[a] Sample of 100 patients

[b] Mean body mass index (BMI)

TABLE 2 Patient and tumor characteristics of patients with initial scan failure (N = 93)

	A	B	C	D	*p*-value
Number of patients	14	5	33	41	
Age (mean in years)	64.7	66.2	64.7	67.0	
BMI (mean in kg/m^2)	29.3	29.1	28.9	28.9	
Tumor size >2 cm	9 (64%)	5 (100%)	15 (45%)	17 (41%)	0.06
Ultrasound axilla (*n*)	1 (7%)	2 (40%)	17 (52%)	23 (56%)	0.007
Axillary metastases (%)	10 (71%)	4 (80%)	17 (52%)	16 (39%)	0.10
Massive nodal/lymphatic tract infiltration	8 (57%)	3 (60%)	3 (9%)	1 (2%)	<0.0001
Axillary recurrence in node-negative patients	–	–	0	0	
Median follow-up node-negative patients (months)	80[a]	49[a]	27	41	

Group A: initial scan failure, no additional tracer given; group B: initial and secondary scan failure; group C: initial scan failure, successful secondary scan; group D: enhanced scan after additional tracer injection

[a] Node-negativity confirmed with ALND

present in three patients only (9%). In 15 patients the SN was found to be tumor-negative and no ALND was performed. No axillary recurrences were noted during a median follow-up of 27 months in these patients. One patient (5.5%, 1/18) in this subgroup had a false-negative SN procedure. A tumor-positive lymph node was found during subsequent simple mastectomy. She was given axillary radiotherapy. No axillary recurrence was seen thereafter within a 60-month follow-up period.

Enhanced Lymphoscintigraphy

In 41 patients (group D, Table 2) with initial scan failure, in which initial lymphoscintigraphy showed only a faint hotspot, judged to be insufficient to allow successful SN harvesting, additional tracer injection led to increased radioactive uptake in the same hotspot (Fig. 3a, b), rather than visualizing additional hotspots. The mean age of these patients was 67.0 years. Additional hotspots as a result of additional tracer injection were seen in only five patients (12%). The increased radioactive uptake facilitated SN harvesting, which was successful in all cases. A tumor-positive SN was found in 16 patients (39%), which was not different from the group of 1,115 patients with clear hotspots on initial lymphoscintigraphy (39%). Only one patient (2.4%) had massive tumor infiltration in the axilla, showing all axillary lymph nodes to be tumor-positive. No completion ALND was performed in the remaining 25 patients with a negative SN biopsy. Among these 25 patients again no axillary recurrences were found during a median follow-up of 41 months.

DISCUSSION

Because of its high sensitivity to detect nodal metastatic disease and its minimally invasive nature, SN biopsy has become the standard of care for staging early invasive breast cancer, thereby limiting axillary dissection to patients with axillary metastases and sparing node-negative patients the morbidity of axillary dissection. However, sometimes the lymphatic mapping procedure tends to fail, because of inadequate or even absent radioisotope uptake in the SN. This urges the surgeon to perform a complete axillary lymph node dissection, which might have been avoided had the lymphatic mapping been successful.

After having experienced 14 patients with a negative preoperative lymphoscintigraphy in the first 3 years of our study, we started to use additional radiocolloid tracer injections as of May 2000, to avoid technical failure of the lymphatic mapping procedure. The use of additional tracer injection has been previously reported by Cserni et al. in 20 patients.[8]

Several factors have been identified to influence lymphatic mapping. Besides technical factors, such as tracer volume, tracer dose, site of tracer injection, and timing of lymphoscintigraphic imaging, other factors such as prior breast surgery and upper lateral tumor location, which might hamper lymphatic mapping due to shine through, have been reported to influence lymphatic drainage patterns. However, there are three major reasons for initial scan failure: extensive nodal tumor infiltration, increased age, and increased body mass index (BMI).

Extensive Nodal Tumor Infiltration

Axillary hotspot visualization is negatively influenced by extensive nodal involvement.[2,9–14] This can be explained by nodal tracer uptake physiology: the radioactive tracer is bound to colloid, which is phagocytosed by macrophages within the normal lymph tissue of the SN. If the SN, or the afferent lymph tracts, show massive tumor infiltration and/or extranodal growth, the lymph flow might be blocked, or there might not be enough functional lymph tissue left to phagocytose the radiocolloid. Thus, if a SN is completely replaced by tumor or the afferent lymph tract is blocked by extensive lymphatic tract infiltration, initial lymphoscintigraphy can fail to show any hotspot. Additional tracer injection under these circumstances might result in secondary scan failure, in which case ALND is mandatory.

Lymphatic tumor burden does not seem to affect blue dye uptake because, in contrast to the uptake of radiocolloid, which is based on sufficient functional lymph tissue, blue dye uptake is a process of passive diffusion through the lymphatic system.[11]

Massive nodal tumor and/or lymphatic tract infiltration was present in 57.1% of 14 patients (group A) early in our study, in which a negative initial lymphoscintigraphy was not followed by additional tracer injection, and in 60% of 5 patients (group B), in whom additional tracer injection, after initial scan failure, did not result in secondary SN visualization.

If additional tracer injection does result in secondary SN visualization, as was seen in 33 patients (group C) in our study, it can be argued whether this visualized hotspot is in fact the true SN, or might be an alternative lymph node which, based on rerouting of lymph flow, is erroneously considered to be the true SN.[13,15,16] If so, rerouting of lymph flow during lymphatic mapping would ultimately result in increased false-negative rates.[17]

However, of 33 patients with secondary SN visualization resulting from additional tracer injection, only 1 patient (5.5%) had a false-negative SN biopsy, whereas 15 patients with a negative SN after additional tracer injection, who consequently had no ALND, showed no axillary recurrences within 29 months of follow-up. These results suggest that SN biopsy after additional tracer injection does not compromise its accuracy, as was also pointed out by others.[18]

Internal Mammary (IM) Basin Drainage

The incidence of IM metastasis is correlated with axillary nodal involvement.[19] It seems intuitive that a large axillary tumor burden can result in blockage of lymph flow to the axilla, consequently leading to redirection of lymph flow to the IM chain.[13] However our results, like those of other investigators, show that extensive nodal infiltration of the axilla is not correlated with increased lymph drainage to the IM lymph nodes, since IM hotspots were noted in only 5.4% (5/93) of patients with initial scan failure, versus 21.2% in patients with a successful initial lymphoscintigraphy (Table 1).[11] This seemingly unexpected result is probably explained by the fact that patients with initial scan failure had a significantly higher mean age and BMI, both of which are inversely correlated to IM lymph drainage.

Palpable Lymph Nodes

An axillary lymph node with gross tumor involvement might consequently be enlarged, and thus is more likely to be detected by routine physical examination and/or axillary ultrasound.

However, because a tumor-loaded lymph node also can be the same size as a tumor-negative lymph node, physical examination of the axillary lymph nodes in order to detect nodal metastases has been shown to be inaccurate.[20,21] Lymph nodes that can be palpated intraoperatively through the incision of the SN biopsy and are felt to be suspicious should be harvested and regarded as SN.[2,22,23]

Axillary Ultrasound

Routine preoperative axillary ultrasound is advocated by several investigators.[9,20,24] Combined with ultrasound-guided FNA of enlarged or suspicious lymph nodes, preoperative ultrasound can detect metastatic disease, hence avoiding an unnecessary or potentially unsuccessful SN biopsy.

In this study, routine preoperative ultrasonography of the axilla, which was introduced in our institute in 2002, was performed in only 43 of the 93 patients with initial scan failure. Moreover, of 48 patients with a tumor-positive axilla in this subgroup, only 15 patients had a preoperative ultrasound examination of the axilla. In one of these patients, ultrasound showed a suspicious lymph node, which was tumor-negative on FNA. Among 15 patients who showed extensive nodal involvement or extranodal tract invasion in relation to initial scan failure (Table 2), preoperative axillary ultrasound was performed in only two patients.

Thus, within this study we were not able to define the diagnostic yield of preoperative axillary ultrasound in relation to initial scan failure.

However, in retrospect, it seems clear that a substantial number of our patients with initial scan failure would not have needed a lymphatic mapping procedure had routine preoperative axillary ultrasonography been introduced earlier in our institute.

Increased Age

With the loss of estrogen levels in postmenopausal women, the breast parenchyma is partially replaced by fatty tissue. This process of fatty degeneration results in a substantial decrease of lymphatic capillaries, normally confined to the breast parenchyma, which in turn is correlated with decreased radioactive uptake in the SN. Thus, increased age is inversely correlated with the ability to visualize axillary hotspots and internal mammary hotspots.[13,25–29]

Likewise, our study showed that the mean age of patients with initial scan failure was significantly higher when compared with patients with a successful initial lymphoscintigraphy (65.8 years versus 58.5 years, $p < 0.0001$).

The inverse effect of increased age on the technical success rate of lymphoscintigraphy becomes even more obvious when looking at the results of 41 patients (group D) in our study with initial scan failure showing only very faint hotspots (Fig. 3), necessitating additional tracer injection for successful SN retrieval. In this subgroup massive nodal tumor infiltration was nearly absent (one patient) and therefore no causal factor for initial scan failure. Subsequently, the increased age in this subgroup (mean 67 years)is the main factor, besides BMI, accountable for non-visualization of hotspots (Table 2).

Body Mass Index (BMI)

BMI is also recognized as a factor that affects lymphoscintigraphic visualization of sentinel nodes.[26,27,30] As is true for increased age, patients with high BMI might have sparse lymphatic capillaries and more fatty tissue in their breast parenchyma.

In our study, mean BMI was 29.0 kg/m^2 for the patients with initial scan failure and 25.5 kg/m^2 for a random sample of 100 patients with clearly visible hotspots on the initial scan. The difference was highly significant ($p < 0.0001$). This result confirms the findings from other investigators regarding the effect of BMI on the success rate of lymphoscintigraphy.

Previous Excisional Biopsy

Previous excisional biopsy is reported to result in change of lymphatic drainage patterns and scan failure.[4,13,31,32] In a previous study, we reported the results of 88 patients, in which SN biopsy with completion ALND was performed following previous excisional biopsy.[33] Initial scan failure was seen in only four patients (4.5%) and no false-negative SN procedures were noted. In the present study 199 patients had a previous excisional biopsy. Of these, 8.0% showed initial scan failure as compared with 7.6% in patients in whom breast cancer was diagnosed by core biopsy (Table 1). Therefore, in our opinion, excisional biopsy prior to SN biopsy is not correlated with scan failure.

CONCLUSION

Sentinel node (SN) biopsy has become the standard of care in the treatment of breast cancer. To prevent unnecessary ALND, the results of preoperative lymphoscintigraphy should be optimal. To avoid technical failure of lymphatic mapping, we evaluated the results and accuracy of additional intracutaneous radiocolloid tracer injections of 37 MBq (1 mCi) in patients with initial scan failure. A negative initial lymphoscintigraphy, if followed by additional tracer injection, resulted in secondary SN visualization in 87% of these patients, thus enabling accurate (false-negative rate 5.5%) SN biopsy. Both age and extensive nodal tumor infiltration as well as BMI adversely affect SN visualization.

In case additional tracer injection does not result in (secondary) SN visualization, ALND is mandatory, because of the high risk of positive lymph nodes, many times with massive tumor infiltration of the axilla.

If initial SN visualization is faint, this is mainly correlated with increased age and high BMI, rather than large tumor burden. In these patients additional tracer injection facilitates an accurate SN procedure.

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REFERENCES

1. Krag DN, Weaver DL, Alex JC, Fairbank JT. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. *Surg Oncol.* 1993;2:335–9.
2. van der Ent FWC, Kengen RAM, van der Pol HAG, Hoofwijk AGM. Sentinel node biopsy in 70 unselected patients with breast cancer: increased feasibility by using 10 mCi radiocolloid in combination with a blue dye tracer. *Eur J Surg Oncol.* 1999;25: 24–9.
3. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg.* 1994;220:391–8.
4. Albertini JJ, Lyman GH, Cox C, et al. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. *JAMA.* 1996;276:1818–22.
5. Borgstein PJ, Meijer S, Pijpers R. Intradermal blue dye to identify sentinel lymph–node in breast cancer. *Lancet.* 1997; 349:1668–9.
6. Tafra L, Lannin DR, Swanson MS, et al. Multicenter trial of sentinel node biopsy for breast cancer using both technetium sulfur colloid and isosulfan blue dye. *Ann Surg.* 2001;233:51–9.
7. Goyal A, Mansel RE. Recent advances in sentinel lymph node biopsy for breast cancer. *Curr Opin Oncol.* 2008;20:621–6.
8. Cserni G, Rajtar M, Boross G, Sinko M, Svebis M, Baltas B. Comparison of vital dye-guided lymphatic mapping and dye plus gamma probe-guided sentinel node biopsy in breast cancer. *World J Surg.* 2002;26:592–7.
9. De Kanter AY, Menke-Pluijmers MB, Henzen-Logmans SC, Van Geel AN, van Eijck CJ, Wiggers T, et al. Reasons for failure to identify positive sentinel nodes in breast cancer patients with significant nodal involvement. *Eur J Surg Oncol.* 2006;32:498–501.
10. Wong SL, Edwards MJ, Chao C, Simpson D, McMasters KM. The effect of lymphatic tumor burden on sentinel lymph node biopsy results. *Breast J.* 2002;8:192–8.

11. Goyal A, Douglas-Jones AG, Newcombe RG, Mansel RE. Effect of lymphatic tumor burden on sentinel lymph node biopsy in breast cancer. *Breast J.* 2005;11:188–94.
12. Noguchi M, Michigishi T, Nakajima K, Koyasaki N, Taniya T, Ohta N, et al. The diagnosis of internal mammary node metastases of breast cancer. *Int Surg.* 1993;78:171–5.
13. Borgstein PJ, Pijpers R, Comans EF, Van Diest PJ, Boom RP, Meijer S. Sentinel lymph node biopsy in breast cancer: guidelines and pitfalls of lymphoscintigraphy and gamma probe detection. *J Am Coll Surg.* 1998;186:275–83.
14. Guenther JM. Axillary dissection after unsuccessful sentinel lymphadenectomy for breast cancer. *Am Surg.* 1995;65:991–4.
15. Kapteijn BA, Nieweg OE, Petersen JL, Rutgers EJ, Hart AA, van Dongen JA, et al. Identification and biopsy of the sentinel lymph node in breast cancer. *Eur J Surg Oncol.* 1998;24:427–30.
16. Noguchi M. Sentinel lymph node biopsy as an alternative to routine axillary lymph node dissection in breast cancer patients. *J Surg Oncol.* 2001;76:144–56.
17. Gulec SA, Moffat FL, Carroll RG, Krag DN. Gamma probe guided sentinel node biopsy in breast cancer. *Q J Nucl Med.* 1997;41:251–61.
18. Bajen MT, Benitez A, Mora J, 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;33:338–43.
19. Cserni G, Szekeres JP. Internal mammary lymph nodes and sentinel node biopsy in breast cancer. *Surg Oncol.* 2001;10:25–33.
20. Lanng C, Hoffmann J, Galatius H, Engel U. Assessment of clinical palpation of the axilla as a criterion for performing the sentinel node procedure in breast cancer. *Eur J Surg Oncol.* 2007;33:281–4.
21. Noguchi M, Katev N, Miyazaki I. Diagnosis of axillary lymph node metastases in patients with breast cancer. *Breast Cancer Res Treat.* 1996;40:283–93.
22. Tanis PJ, Nieweg OE, Merkus JW, Peterse JL, Kroon BB. False negative sentinel node procedure established through palpation of the biopsy wound. *Eur J Surg Oncol.* 2000;26:714–5.
23. Gui GP, Joubert DJ, Reichert R, et al. Continued axillary sampling is unnecessary and provides no further information to sentinel node biopsy in staging breast cancer. *Eur J Surg Oncol.* 2005;31:707–14.
24. van Rijk MC, Deurloo EE, Nieweg OE, et al. Ultrasonography and fine-needle aspiration cytology can spare breast cancer patients unnecessary sentinel lymph node biopsy. *Ann Surg Oncol.* 2006;13:31–5.
25. Heuts EM, van der Ent FW, van der Pol HA, et al. Evaluation of early versus delayed lymphoscintigraphic imaging in detecting internal mammary sentinel lymph nodes in breast cancer: a multicenter study to establish an optimal lymphatic mapping protocol. *Nucl Med Commun.* 2006;27:677–81.
26. 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;32:286–93.
27. Cox CE, Dupont E, Whitehead GF, et al. Age and body mass index may increase the chance of failure in sentinel lymph node biopsy for women with breast cancer. *Breast J.* 2002;8:88–91.
28. 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;41:1500–6.
29. McMasters KM, Tuttle TM, Carlson DJ, et al. Sentinel lymph node biopsy for breast cancer: a suitable alternative to routine axillary dissection in multi-institutional practice when optimal technique is used. *J Clin Oncol.* 2000;18:2560–6.
30. Derossis AM, Fey JV, Cody HS III, Borgen PI. Obesity influences outcome of sentinel lymph node biopsy in early-stage breast cancer. *J Am Coll Surg.* 2003;197:896–901.
31. Estourgie SH, Valdes Olmos RA, Nieweg OE, Hoefnagel CA, Rutgers EJ, Kroon BB. Excision biopsy of breast lesions changes the pattern of lymphatic drainage. *Br J Surg.* 2007;94:1088–91.
32. Glass EC, Essner R, Giuliano AE. Sentinel node localization in breast cancer. *Semin Nucl Med.* 1999;29:57–68.
33. Heuts EM, van der Ent FW, Kengen RA, van der Pol HA, Hulsewe KW, Hoofwijk AG. Results of sentinel node biopsy not affected by previous excisional biopsy. *Eur J Surg Oncol.* 2006;32:278–81.