MULTIDISCIPLINARY SYMPOSIUM: BREAST CANCER

Monday 3 October 2005, 08:45–10:45

The sentinel node in breast cancer: an update

Conor D Collins

St Vincent’s University Hospital, Dublin, Ireland

Corresponding address: Conor D Collins, St Vincent’s University Hospital, Dublin 4, Ireland
E-mail: c.collins@st-vincents.ie

Abstract

There has been rapid acceptance of sentinel lymph node biopsy into the management of breast cancer over the past 10 years. This article seeks to highlight the controversies and to summarise its current status.

Keywords: Sentinel lymph node; breast cancer.

Introduction

The prognosis of breast cancer is determined primarily by axillary lymph node status[1–3]. Axillary lymph node dissection (ALND) surgery carries a significant morbidity with complications such as lymphoedema, pain, numbness and limited shoulder movement[4–6]. The sentinel node is the first draining node on the direct drainage pathway from the primary tumour site[7]. If the sentinel node is positive there is a 40% risk that higher order nodes may also be involved with metastatic disease[8]. Sentinel lymph node biopsy (SLNB) is a minimally invasive alternative to ALND for nodal staging in breast cancer. The technique assumes orderly progression of tumour spread to the regional nodes; and biopsy of the first node in the lymphatic chain at risk for metastasis should therefore reflect involvement of the remaining nodes. Although no results from randomised trials validating SLN biopsy in breast cancer are yet available, excellent clinical outcomes using different protocols have been achieved in over 20,000 patients studied to date[8]. Comparison of the results of SLNB with ALND has shown that the sentinel node is representative of the presence or absence of metastases in the remainder of the nodal basin (with a false negative rate of less than 2% in most series)[9–13]. Other prospective studies have also validated the concept[14–18].

Technical issues

Lymphoscintigraphy

A large choice of dyes and radiopharmaceuticals (usually $^{99m}$Tc sulphur colloid) are available. The colloid employed should be of a size to be taken up efficiently and retained within the sentinel node. It has been shown that the highest counts in recovered sentinel nodes were from 100–200 nm albumin colloid particles[19]. Filtered $^{99m}$Tc sulphur colloid (100 nm filtered) has a faster transport rate to the regional nodes and lower radiation dosimetry. As a result it is the preferred choice if performing surgery within 2 h of injection[8]. The sentinel node is more successfully identified with radiopharmaceuticals than with dyes but a combined technique using both maximises the potential of accurate staging[15,20–22]. Preoperative lymphoscintigraphy enables faster location of radioactive nodes at surgery and the combined approach results in identification and harvesting of more nodes[23,24]. The injection technique seems to matter little as axillary nodes stained blue by intradermal, peritumoural, subdermal, periareolar and subareolar injections identify the same nodes[21,25–27]. It also appears that there is often more than one sentinel lymph node and using dual agents will assist in identifying all sentinel nodes. In a prospective multi-institutional study of 1436 patients, the false negative rate was 14.3% if a single sentinel lymph node was removed compared with 4.3% if multiple sentinel lymph nodes were removed indicating that there is often more
than one sentinel node[28]. Despite variation in mapping
techniques results have been similar worldwide with
sensitivity and diagnostic accuracy rates greater than 95%
and false negative rates ranging from 0 to 10%[29]. Some
breast cancer programmes do not routinely utilize preop-
erative lymphoscintigraphy because of the added time,
expense and the fact that the surgical decision making
can be performed intraoperatively[3]. Others advocate the
concept of the triple technique comprising preoperative
lymphoscintigraphy, and injection of radiotracer with
the use of a hand probe and blue dye[30]. Variables
such as availability of resources, patient numbers,
level of competence and local working practices mean
that no standard protocol exists. Nonetheless, it is
recognised that identification of the sentinel node in
greater than 96% of patients and a false negative rate
of less than 5% is a desirable outcome[10,31,32]. Using
lymphoscintigraphy the surface location of the sentinel
node can be marked with some centres marking all
sentinel nodes visualised[33,34]. Although high resolution
collimators should be used, a medium energy collimator
will suffice[34]. The camera is placed as close to the
patient as possible and images should be acquired in
at least two planes. If the site of injection is close to
the nodes, shielding may be necessary to visualise the
sentinel node. In one centre analysing the results
of 640 patients, 94% demonstrated a sentinel node in
the ipsilateral axilla but 46% also had sentinel nodes
outside the axilla[34]. The most important site of extra-
axillary drainage was to the internal mammary nodal
chain and 40% of patients demonstrated a sentinel
node in this area[34]. In 5% of patients, drainage was
exclusively to extra-axillary sentinel nodes. Preoperative
lymphoscintigraphy enables these nodes to be identified.

Site of injection
Several theories exist concerning lymph node drainage in
the human breast[35]. Although Sappey described flow
to the subareolar plexus and then to the axilla, this
view was not universally accepted[36]. An alternative
drainage pattern proposed direct drainage to the ipsi-
lateral axilla avoiding the subareolar plexus[35,37]. A
recent study of 145 dynamic lymphoscintigrams using
both intraparenchymal and subdermal injections was
unable to visualise the subareolar plexus indicating
that it may not act as a conduit to the ipsilateral
axilla[38]. Variable drainage patterns from injections of
localising agents into the subareolar plexus, subdermal
breast tissue and the deep breast parenchyma have been
demonstrated by several groups[39-42]. Seven sites of
injection have been described (peritumoural, subdermal,
periareolar, intratumoural, intradermal, subareolar and
subtumoural) and one of the factors dictating choice is
the intention to locate internal mammary nodes in
addition to axillary nodes[143]. Peritumoural injections
were the first type of injection used[44,45]. Some groups
claim better success with intradermal injections than with
peritumoural technique when sulphur colloid and blue
dye are used[46]. Internal mammary node drainage occurs
in a significant proportion after peritumoural injection
but not after intradermal injection[47]. However, the
intradermal technique has been shown to identify the
SLN in the axilla with a frequency of 98% compared
with 90% for peritumoural parenchymal technique[10,48].
Periareolar injections are made just outside the areolar
border at four equally spaced sites. The injections
are subdermal though a single subareolar injection
lined up with the tumour can also be used[26,27,49].
This technique militates against extra-axillary node
identification but is easy and efficient[50-52]. Using a
combination of radioisotope and blue dye, the SLN
was identified successfully in 98% of cases with no
false negative results[53]. Subareolar injection of blue
dye alone has been shown to demonstrate a sentinel
lymph node in 98% of cases with no false negative sentinel
des[50,54]. Likewise, it has been shown that
subareolar injection of technetium is equivalent to
peritumoural injection of blue dye[55,56]. One centre
uses the combined intraparenchymal and subdermal
injection technique because it more accurately reflects all
lymphatic flow from breast tumour[38]. Intraparenchymal
injections consistently visualise a more diverse pattern of
lymph flow. In particular, the internal mammary chains
and supraclavicular nodes are commonly seen after
intraparenchymal injection but rarely after subareolar
or subdermal injections. Peritumoural and subdermal
injection of 99mTc sulphur colloid combined with
periareolar injection of isosulphan blue dye is advocated
by another group with extensive experience[32,57-59].
Overall, the identification rate, accuracy and predictive
value of sentinel node biopsy seem to be unaffected by the
site of injection though a difference may become apparent
with long-term follow-up that examines the pattern of
axillary failure correlated with the injection site[13].

When should injection be performed?
Comparable accuracies have been shown for same day
and day before surgery radioisotope injections[60,61].
After injection breast massage may be performed to
augment lymphatic flow[62]. However, concern exists
that tumour cells might be transported from the primary
tumour into the lymphatics. Pressure within the lymph-
atics can increase up to 22-fold following external massage
and transport of tumour cells to the lymphatic spaces has
been demonstrated[63-65]. However, isolated tumour cells
are not true metastases and do not have malignant poten-
tial. Intraoperative injection is little used as it requires
transfer of radioisotope to the operating theatre, is not as
reliable and is complicated by radiation safety issues.

Pathology
The role of the pathology laboratory is pivotal to the
success of the procedure. In particular the development
of multisectioning and immunohistochemistry (IHC) staining techniques has been reported to increase the rate of detection of malignant disease by up to 33%.[66–68] IHC can be particularly beneficial in patients with invasive lobular cancer.[69,70]. Trials currently in progress aim to determine the significance of IHC detected micrometastases in patients treated by conventional pathological criteria.[71]. It has been shown recently that patients with favourable breast cancer histology have only a small risk of axillary sentinel lymph node metastases and that biopsy is not necessary in all these patients.[72].

Radiation safety

Several papers have discussed various aspects of radiation safety associated with the sentinel node in detail.[73–78]. Radiation doses are low and no additional procedures are required for the protection of staff. The procedure can be performed safely during pregnancy as the foetal dose is very low.

Clinical issues

The procedure is not contraindicated in patients with clinically palpable axillary nodes.[18]. Relative contraindications include prior axillary surgery and subglandular breast implants. In one centre, more than 50 patients with subpectoral implants have been associated with 100% SLN identification success rate and no clinically detected recurrences in patients with negative SLN biopsy.[8]. For patients with a primary tumour greater than 4 cm, the success of SLNB shows little difference to those with smaller tumours.[12]. In patients with multifocal breast cancer, sentinel node identification has been reported in 94% and is an accurate predictor of nodal status.[79]. This type of cancer favours a periareolar or subareolar injection protocol. SLNB performed following excisional biopsy demonstrates satisfactory results.[29,80]. Patients with ductal carcinoma-in-situ (DCIS) have an excellent long term prognosis (98% survival) but 10%–29% of these patients will have invasive cancer at definitive surgery.[81–87]. Analysis of resected nodes from patients who had negative axillary surgery previously, demonstrated micrometastases in 13% of nodes but none in patients who had disease recurrence.[88]. This would indicate that SNLB is not necessary in these patients.

False negative rate

The false negative rate is the percentage of node positive patients who are missed by mapping.[88]. In one centre there has been no axillary recurrence (mean 5 years) following a negative node biopsy in 1914 patients.[8]. Data from case control studies to date indicate SLN biopsy to be highly predictive of axillary node status with a false negative rate of less than 5%.[89]. Reasons for false negative results are attributed to changes in surgical personnel, difficult lymph node location and absence of a thorough histological study.[90]. Factors militating against sentinel node identification are increasing age and body mass index.[91]. A review of ten large observational studies revealed just ten axillary recurrences in 2664 patients (0.4%) who did not undergo ALND following negative SLN biopsy.[43]. A large recent study comprising 4008 patients and a median follow-up of 31 months had an overall axillary recurrence rate of 0.25%.[92]. A further study in 234 patients (median follow-up 42 months) did not find an increased rate of axillary recurrence in patients with negative SLN or SLN micrometastases.[93]. As the axillary recurrence rate should not exceed that seen after conventional axillary clearance surgery (1.0%–2.3%), the figures quoted above compare very favourably.[94–96].

Internal mammary and intramammary lymph nodes

Intramammary nodes with metastases have been documented as independent predictors of poor outcome for patients with breast cancer.[97]. In one centre analysing the results of 640 patients, 94% demonstrated a sentinel node in the ipsilateral axilla and 46% also had sentinel nodes outside the axilla.[34]. In 5% of patients drainage was exclusively to non-axillary sentinel nodes. The most important non-axillary drainage was to the internal mammary nodal chain and 40% of patients demonstrated a sentinel node in this area.[34]. Sentinel lymph node biopsy of internal mammary nodes is associated with a low morbidity and has been shown to improve staging and change treatment strategy.[98,99]. Proponents of evaluating internal mammary nodes argue that this supports lymphatic mapping as it provides more accurate staging although its impact on outcome is less clear.[100,101]. Nonetheless, it has been demonstrated that metastases in the internal mammary nodes influence survival in a manner comparable to that of metastases in axillary lymph nodes.[102]. A review with 30 years of results demonstrated that patients with isolated IMN disease have a prognosis equivalent to that of patients with isolated axillary metastases.[103]. A combination of metastatic disease in both axillary and internal mammary nodal chains has an especially poor prognosis with a 10-year survival of 37%.[104]. Internal mammary nodes identified on preoperative lymphoscintigraphy require histopathological confirmation of disease before therapy is commenced.[105]. Internal mammary nodes are best identified when peritumoural, intratumoural or subcutaneous injections are made with some reports visualising these nodes in 10%–30% of patients whereas subdermal, intradermal, periareolar or subareolar injections result in much less frequent visualisation of these nodes.[47,58].

Micrometastases

Micrometastases are defined as tumour deposits in nodes ranging from 0.2 to 2 mm with cells less than 0.2 mm known as isolated tumour cells.[106]. Despite
the evidence of some retrospective studies there is controversy regarding the prognostic significance of micrometastases found only by immunohistochemistry staining, particularly when only isolated tumour cells are found. A literature review on the clinical significance of micrometastases concluded that they were associated with a poorer prognosis than that associated with an axillary involvement. In a study involving a 15-year follow-up on almost 100 patients and 1539 axillary lymph nodes with pT1 breast cancer determined that half of the patients developed distant metastases. However, recent studies involving 234 patients and 84 patients (median follow-up 42 and 40 months, respectively) showed that micrometastases were not associated with an increased risk of axillary recurrence or that outcome was significantly affected by the presence of micrometastases. Micrometastases are not reliably detected by FDG-PET imaging.

### Neoadjuvant therapy

In published work to date the SLN identification rate has ranged from 84% to 97% implying that the accuracy of sentinel node biopsy is not influenced by neoadjuvant therapy. Questions remain as to whether all nodes respond equally to therapy and a high false negative rate (up to 33%) has been reported in some of these series. Pending further clarification, it is still probably best to perform SLNB prior to commencement of neoadjuvant therapy.

### Summary

Lymphatic mapping for breast cancer is rapidly becoming the standard of care but there is no single study that demonstrates conclusively which particular sentinel node protocol is best for a specific patient. The results from three multicentre trials sponsored by the National Cancer Institute (due to report in 2007) attempting to answer some of the issues discussed above are eagerly awaited.

### References

[1] Fisher ER, Costantino J, Fisher B, Redmond C. Pathologic findings from the National Surgical Adjuvant Breast Project (Protocol 4). Discriminants for 15-year survival. National Surgical Adjuvant Breast and Bowel Project Investigators. Cancer 1993; 71: 2141–50.

[2] Fitzgibbons PL, Page DL, Weaver D et al. Prognostic factors in breast cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med 2000; 124: 966–78.

[3] Singletary SE, Allred C, Ashley P et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol 2002; 20: 3628–36.

[4] Warmuth MA, Bowen G, Prosnitz LR et al. Complications of axillary lymph node dissection for carcinoma of the breast: a report based on a patient survey. Cancer 1998; 83: 1362–8.

[5] Hack TF, Cohen L, Katz J, Robson LS, Goss P. Physical and psychological morbidity after axillary lymph node dissection for breast cancer. J Clin Oncol 1999; 17: 143–9.

[6] Schenk P, Rieger R, Shamiyeh A, Wayand W. Morbidity following sentinel lymph node biopsy versus axillary lymph node dissection for patients with breast carcinoma. Cancer 2000; 88: 608–14.

[7] Morton DL, Bostick PJ. Will the true sentinel node please stand? Ann Surg Oncol 1999; 6: 12–4.

[8] Jakub JW, Cox CE, Pippas AW, Gardner M, Pendas S, Reintgen DS. Controversial topics in breast lymphatic mapping. Semin Oncol 2004; 31: 324–32.

[9] Kapteijn BA, Nieweg OE, Petersen JL et al. Identification and biopsy of the sentinel lymph node in breast cancer. Eur J Surg Oncol 1998; 24: 427–30.

[10] McMasters KM, Wong SL, Chao C et al. Defining the optimal surgeon experience for breast cancer sentinel lymph node biopsy: a model for implementation of new surgical techniques. Ann Surg 2001; 234: 292–9; discussion 299–300.

[11] Krag DN, Harlow S. Current status of sentinel node surgery in breast cancer. Oncology (Williston Park) 2003; 17: 1663–6; discussion 1669–70, 1675–6.

[12] Jakub JW, Pendas S, Reintgen DS. Current status of sentinel lymph node mapping and biopsy: facts and controversies. Oncologist 2003; 8: 59–68.

[13] Chao C, Wong SL, Tuttle TM et al. Sentinel lymph node biopsy for breast cancer: improvement in results over time. Breast J 2004; 10: 337–44.

[14] Giuliano AE, Jones RC, Brennan M, Statman R. Sentinel lymphadenectomy in breast cancer. J Clin Oncol 1997; 15: 2345–50.

[15] Krag D, Weaver D, Ashikaga T et al. The sentinel node in breast cancer – a multicenter validation study. N Engl J Med 1998; 339: 941–6.

[16] 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.

[17] Liberman L, Cody HS 3rd, Hill AD et al. Sentinel lymph node biopsy after percutaneous diagnosis of nonpalpable breast cancer. Radiology 1999; 211: 835–44.

[18] Specht MC, Fey JV, Borgen PI, Cody HS 3rd. Is the clinically positive axilla in breast cancer really a contraindication to sentinel lymph node biopsy? J Am Coll Surg 2005; 200: 10–4.

[19] Edreira MM, Colombo LL, Perez JH, Sajaroff EO, de Castiglia SG. In vivo evaluation of three different 99mTc-labelled radiopharmaceuticals for sentinel lymph node identification. Nucl Med Commun 2001; 22: 499–504.

[20] Derossis AM, Fey J, Yeung H et al. A trend analysis of the relative value of blue dye and isotope localization in 2,000 consecutive cases of sentinel node biopsy for breast cancer. J Am Coll Surg 2001; 193: 473–8.

[21] Radovanovic Z, Golubovic A, Pizlak A, Stojiljkovic B, Radovanovic D. Blue dye versus combined blue dye-radioactive tracer technique in detection of sentinel lymph node in breast cancer. Eur J Surg Oncol 2004; 30: 913–7.

[22] Pelosi E, Ala A, Bello M et al. Impact of axillary nodal metastases on lymphatic mapping and sentinel lymph
node identification rate in patients with early stage breast cancer. Eur J Nucl Med Mol Imaging 2005; Epub ahead of print.

[23] Mariani G, MoreSCO L, Viale G et al. Radioguided sentinel lymph node biopsy in breast cancer surgery. J Nucl Med 2001; 42: 1198–215.

[24] Motomura K, Noguchi A, Hashizume T et al. Usefulness of a solid-state gamma camera for sentinel node identification in patients with breast cancer. J Surg Oncol 2005; 89: 12–7.

[25] 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: 81–9.

[26] Pelosi E, Baiocco C, Ala A et al. Lymphatic mapping in early stage breast cancer: comparison between periareolar and subdermal injection. Nucl Med Commun 2003; 24: 519–23.

[27] Pelosi E, Bello M, Giors M et al. Sentinel lymph node detection in patients with early-stage breast cancer: comparison of periareolar and subdermal/peritumoral injection techniques. J Nucl Med 2004; 45: 220–5.

[28] Wong SL, Edwards MJ, Chao C et al. Sentinel lymph node biopsy for breast cancer: impact of the number of sentinel nodes removed on the false-negative rate. J Am Coll Surg 2001; 192: 684–9; discussion 689–91.

[29] Pendas S, Giuliano R, Swor G, Gardner M, Jakub J, Reintgen DS. Worldwide experience with lymphatic mapping for invasive breast cancer. Semin Oncol 2004; 31: 318–23.

[30] Torrenga H, Meijer S, Fabry H, van der Sijp J. Sentinel node biopsy in breast cancer patients: triple technique as a routine procedure. Ann Surg Oncol 2004; 11: S231–5.

[31] Cox CE, Salud CJ, Cantor A et al. Learning curves for breast cancer sentinel lymph node mapping based on surgical volume analysis. J Am Coll Surg 2001; 193: 593–600.

[32] Aarsvold JN, Alazraki NP. Update on detection of sentinel lymph nodes in patients with breast cancer. Semin Nucl Med 2005; 35: 116–28.

[33] Uren RF, Thompson JF, Howman-Giles R. Lymphatic drainage of the skin and breast: locating the sentinel nodes. Amsterdam: Harwood Academic, 1999.

[34] Uren RF, Howman-Giles R, Chung D, Thompson JF. Nuclear medicine aspects of melanoma and breast lymphatic mapping. Semin Oncol 2004; 31: 338–48.

[35] Tanis PJ, Nieweg OE, Valdes Olmos RA, Kroon BB. Anatomy and physiology of lymphatic drainage of the breast from the perspective of sentinel node biopsy. J Am Coll Surg 2001; 192: 399–409.

[36] Turner-Warwick RT. The lymphatics of the breast. Br J Surg 1959; 46: 574–82.

[37] Shen P, Glass EC, DiFronzo LA, Giuliano AE. Dermal versus intraparenchymal lymphoscintigraphy of the breast. Ann Surg Oncol 2001; 8: 241–8.

[38] Kaleya RN, Heckman JT, Most M, Zager JS. Lymphatic mapping and sentinel node biopsy: a surgical perspective. Semin Nucl Med 2005; 35: 129–34.

[39] Nieweg OE, Jansen L, Valdes Olmos RA et al. Lymphatic mapping and sentinel lymph node biopsy in breast cancer. Eur J Nucl Med 1999; 26: S11–6.

[40] Canavese G, Gipponi M, Catturich A et al. Pattern of lymphatic drainage to the sentinel lymph node in breast cancer patients. J Surg Oncol 2000; 74: 69–74.

[41] Byrd DR, Dunnwald LK, Mankoff DA et al. Internal mammary lymph node drainage patterns in patients with breast cancer documented by lymphoscintigraphy. Ann Surg Oncol 2001; 8: 234–40.

[42] Estourgie SH, Nieweg OE, Olmos RA, Rutgers EJ, Kroon BB. Lymphatic drainage patterns from the breast. Ann Surg 2004; 239: 232–7.

[43] Nieweg OE, Estourgie SH, van Rijk MC, Kroon BB. Rationale for superficial injection techniques in lymphatic mapping in breast cancer patients. J Surg Oncol 2004; 87: 153–6.

[44] Giuliano AE, Kirkan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg 1994; 220: 391–8; discussion 398–401.

[45] 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.

[46] Lin KM, Patel TH, Ray A et al. Intradermal radioisotope is superior to peritumoral blue dye or radioisotope in identifying breast cancer sentinel nodes. J Am Coll Surg 2004; 199: 561–6.

[47] Park C, Seid P, Morita E et al. Internal mammary sentinel lymph node mapping for invasive breast cancer: implications for staging and treatment. Breast J 2005; 11: 29–33.

[48] Borgstein PJ, Meijer S, Pijpers R. Intradermal blue dye to identify sentinel lymph-node biopsy in breast cancer. Lancet 1997; 349: 1668–9.

[49] Krynychky BR, Kim CK, Mosci K et al. Areolar-cutaneous ‘junction injections’ to augment sentinel node count activity. Clin Nucl Med 2003; 28: 97–107.

[50] Kern KA. Lymphoscintigraphic anatomy of sentinel lymphatic channels after subareolar injection of Technetium 99m sulfur colloid. J Am Coll Surg 2001; 193: 601–8.

[51] Kern KA. Breast lymphatic mapping using subareolar injections of blue dye and radiocolloid: illustrated technique. J Am Coll Surg 2001; 192: 545–50.

[52] Vargas HI, Tolmos J, Agbunan RG et al. A validation trial of subdermal injection compared with intraparenchymal injection for sentinel lymph node biopsy in breast cancer. Am Surg 2002; 68: 87–91.

[53] Kern KA. Concordance and validation study of sentinel node biopsy for breast cancer using subareolar injection of blue dye and technetium 99m sulfur colloid. J Am Coll Surg 2002; 195: 467–75.

[54] Kern KA. Sentinel lymph node mapping in breast cancer using subareolar injection of blue dye. J Am Coll Surg 1999; 189: 539–45.

[55] Klimberg VS, Rubio IT, Henry R, Cowan C, Colvert M, Korourian S. Subareolar versus peritumoral injection for location of the sentinel lymph node. Ann Surg 1999; 229: 860–4; discussion 864–5.

[56] Chagpar A, Martin RC 3rd, Chao C et al. Validation of subareolar and periareolar injection techniques for breast sentinel lymph node biopsy. Arch Surg 2004; 139: 614–8; discussion 618–20.

[57] Alazraki NP, Styblo T, Grant SF, Cohen C, Larsen T, Aarsvold JN. Sentinel node staging of early breast cancer using lymphoscintigraphy and the intraoperative gamma-
detecting probe. Semin Nucl Med 2000; 30: 56–64.

[58] Alazraki NP, Styblo T, Grant SF et al. Sentinel node staging of early breast cancer using lymphoscintigraphy and the intraoperative gamma detecting probe. Radiol Clin North Am 2001; 39: 947–96, viii.

[59] Styblo T, Aarsvold JN, Grant SF et al. Sentinel lymph nodes: optimizing success. Semin Roentgenol 2001; 36: 261–9.

[60] McCarter MD, Yeung H, Yeh S, Fey J, Borgen PL, Cody HS 3rd. Localization of the sentinel node in breast cancer: identical results with same-day and day-before isotope injection. Ann Surg Oncol 2001; 8: 682–6.

[61] Babiera GV, Delpassand ES, Breslin TM et al. Lymphatic drainage patterns on early versus delayed breast lymphoscintigraphy performed after injection of filtered Tc-99m sulfur colloid in breast cancer patients undergoing sentinel lymph node biopsy. Clin Nucl Med 2005; 30: 11–5.

[62] Bass SS, Cox CE, Salud CJ et al. The effects of postinjection massage on the sensitivity of lymphatic mapping in breast cancer. J Am Coll Surg 2001; 192: 9–16.

[63] Ikomi F, Hunt J, Hanna G, Schmid-Schonbein GW. Interstitial fluid, plasma protein, colloid, and leukocyte uptake into initial lymphatics. J Appl Physiol 1996; 81: 2060–7.

[64] Carter BA, Jensen RA, Simpson JF, Page DL. Benign transport of breast epithelium into axillary lymph nodes after biopsy. Am J Clin Pathol 2000; 113: 259–65.

[65] Diaz NM, Cox CE, Ebert M et al. Benign mechanical transport of breast epithelial cells to sentinel lymph nodes. Am J Surg Pathol 2004; 28: 1641–5.

[66] Dowlatshahi K, Fan M, Snider HC, Habib FA. Lymph node micrometastases from breast carcinoma: reviewing the dilemma. Cancer 1997; 80: 1188–97.

[67] Turner RR, Chu KU, Qi K et al. Pathologic features associated with nonsentinel lymph node metastases in patients with metastatic breast carcinoma in a sentinel lymph node. Cancer 2000; 89: 574–81.

[68] Cohen C, Alazraki N, Styblo T, Waldrop SM, Grant SF, Larsen T. Immunohistochemcial evaluation of sentinel lymph nodes in breast carcinoma patients. Appl Immunohistochem Mol Morphol 2002; 10: 296–303.

[69] Trojani M, de Mascarel I, Coindre JM, Bonichon F. Micrometastases to axillary lymph nodes from invasive lobular carcinoma of breast: detection by immunohistochemistry and prognostic significance. Br J Cancer 1987; 56: 838–9.

[70] Cote RJ, Peterson HF, Chaiwun B et al. Role of immunohistochemical detection of lymph-node metastases in management of breast cancer. International Breast Cancer Study Group. Lancet 1999; 354: 896-900.

[71] Quan ML, Cody HS 3rd. Missed micrometastatic disease in breast cancer. Semin Oncol 2004; 31: 311–7.

[72] Mendez JE, Fey JV, Cody H, Borgen PI, Sclafani LM. Can sentinel lymph node biopsy be omitted in patients with favorable breast cancer histology? Ann Surg Oncol 2005; 12: 24–8.

[73] Fitzgibbons PL, LiVolsi VA. Recommendations for handling radioactive specimens obtained by sentinel lymphadenectomy. Surgical Pathology Committee of the College of American Pathologists, and the Association of Directors of Anatomic and Surgical Pathology. Am J Surg Pathol 2000; 24: 1549–51.

[74] Nugent N, Hill AD, Casey M et al. Safety guidelines for radiolocalised sentinel node resection. Ir J Med Sci 2001; 170: 236–8.

[75] Morton R, Horton PW, Peet DJ, Kissin MW. Quantitative assessment of the radiation hazards and risks in sentinel node procedures. Br J Radiol 2003; 76: 117–22.

[76] Gentilini O, Cremonesi M, Trifiro G et al. Safety of sentinel node biopsy in pregnant patients with breast cancer. Ann Oncol 2004; 15: 1348–51.

[77] Michel R, Hofer C. Radiation safety precautions for sentinel lymph node procedures. Health Phys 2004; 86: S35–7.

[78] Law M, Chow LW, Kwong A, Lam CK. Sentinel lymph node technique for breast cancer: radiation safety issues. Semin Oncol 2004; 31: 298–303.

[79] Toussimis E, Van Zee KJ, Fey JV et al. The accuracy of sentinel lymph node biopsy in multicentric and multifocal invasive breast cancers. J Am Coll Surg 2003; 197: 529–35.

[80] Haigh PL, Hansen NM, Qi K, Giuliano AE. Biopsy method and excision volume do not affect success rate of subsequent sentinel lymph node dissection in breast cancer. Ann Surg Oncol 2000; 7: 21–7.

[81] Cox CE, Nguyen K, Gray RJ et al. Importance of lymphatic mapping in ductal carcinoma in situ (DCIS): why map DCIS? Am Surg 2001; 67: 513–9; discussion 519–21.

[82] Burak WE Jr, Owens KE, Tighe MB et al. Vacuum-assisted stereotactic breast biopsy: histologic underestimation of malignant lesions. Arch Surg 2000; 135: 700–3.

[83] Lee CH, Carter D, Philipotts LE et al. Ductal carcinoma in situ diagnosed with stereotactic core needle biopsy: can invasion be predicted? Radiology 2000; 217: 466–70.

[84] Klauber-DeMore N, Tan LK, Liberman L et al. Sentinel lymph node biopsy: is it indicated in patients with high-risk ductal carcinoma in situ and ductal carcinoma-in-situ with microinvasion? Ann Surg Oncol 2000; 7: 636–42.

[85] Darling ML, Smith DN, Lester SC et al. Atypical ductal hyperplasia and ductal carcinoma in situ as revealed by large-core needle breast biopsy: results of surgical excision. AJR Am J Roentgenol 2000; 175: 1341–6.

[86] Renshaw AA. Predicting invasion in the excision specimen from breast core needle biopsy specimens with only ductal carcinoma in situ. Arch Pathol Lab Med 2002; 126: 39–41.

[87] Mendez I, Andreu FJ, Saez E et al. Ductal carcinoma in situ and atypical ductal hyperplasia of the breast diagnosed at stereotactic core biopsy. Breast J 2001; 7: 14–8.

[88] Lara JF, Young SM, Velilla RE, Santoro EJ, Templeton SF. The relevance of occult axillary micrometastasis in ductal carcinoma in situ: a clinicopathologic study with long-term follow-up. Cancer 2003; 98: 2105–13.

[89] Mansel RE, Goyal A. European studies on breast lymphatic mapping. Semin Oncol 2004; 31: 304–10.

[90] Vidal-Sicart S, Pons F, Puig S et al. Identification of the sentinel lymph node in patients with malignant melanoma: what are the reasons for mistakes? Eur J Nucl Med Mol Imaging 2003; 30: 362–6.

[91] Cox CE, Dupont E, Whitehead GP 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.

[92] Naik AM, Fey J, Gemignani M et al. The risk of axillary relapse after sentinel lymph node biopsy for breast cancer is comparable with that of axillary lymph node dissection: a follow-up study of 4008 procedures. Ann Surg 2004; 240: 462–8; discussion 468–71.

[93] Langer I, Marti WR, Guller U et al. Axillary recurrence rate in breast cancer patients with negative sentinel lymph node (SLN) or SLN micrometastases: prospective analysis of 150 patients after SLN biopsy. Ann Surg 2005; 241: 152–8.

[94] Recht A, Pierce SM, Abner A et al. Regional nodal failure after conservative surgery and radiotherapy for early-stage breast carcinoma. J Clin Oncol 1991; 9: 988–96.

[95] Fredriksson I, Liljegren G, Arnesson LG et al. Consequences of axillary recurrence after conservative breast surgery. Br J Surg 2002; 89: 902–8.

[96] Nieweg OE, van Rijk MC, Valdes Olmos RA, Hoefnagel CA. Sentinel node biopsy and selective lymph node clearance-impact on regional control and survival in breast cancer and melanoma. Eur J Nucl Med Mol Imaging 2005; 32: 631–4.

[97] Shen J, Hunt KK, Mirza NQ et al. Intramammary lymph node metastases are an independent predictor of poor outcome in patients with breast carcinoma. Cancer 2004; 101: 1330–7.

[98] 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 2002; 87: 705–10.

[99] Noguchi M. Relevance and practicality of internal mammary sentinel node biopsy for breast cancer. Breast Cancer 2002; 9: 329–36.

[100] 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 2002; 9: 924–8.

[101] Fabry HF, Mutsaers PG, Meijer S et al. Clinical relevance of parasternal uptake in sentinel node procedure for breast cancer. J Surg Oncol 2004; 87: 13–8.

[102] Bevilacqua JL, Gucciaro G, Cody HS et al. A selection algorithm for internal mammary sentinel lymph node biopsy in breast cancer. Eur J Surg Oncol 2002; 28: 603–14.

[103] 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 1999; 35: 1320–5.

[104] Veronesi U, Cascinelli N, Bufalino R et al. Risk of internal mammary lymph node metastases and its relevance on prognosis of breast cancer patients. Ann Surg 1983; 198: 681–4.

[105] Benda RK, Cendan JC, Copeland EM et al. Should decisions on internal mammary lymph node irradiation be based on current lymphoscintigraphy techniques for sentinel lymph node identification? Cancer 2004; 100: 518–23.

[106] Hermanek P, Hutter RV, Sobin LH, Wittekind C. International Union Against Cancer. Classification of isolated tumor cells and micrometastasis. Cancer 1999; 86: 2668–73.

[107] Sakorafas GH, Geraghty J, Pavlakis G. The clinical significance of axillary lymph node micrometastases in breast cancer. Eur J Surg Oncol 2004; 30: 807–16.

[108] Susnik B, Frkovic-Grazio S, Bracko M. Occult micrometastases in axillary lymph nodes predict subsequent distant metastases in stage I breast cancer: a case-control study with 15-year follow-up. Ann Surg Oncol 2004; 11: 568–72.

[109] Changp A, Middleton LP, Sahin AA et al. Clinical outcome of patients with lymph node-negative breast carcinoma who have sentinel lymph node micrometastases detected by immunohistochromy. Cancer 2005; 103: 1581–6.

[110] Lovrics PJ, Chen V, Coates G et al. A prospective evaluation of positron emission tomography scanning, sentinel lymph node biopsy, and standard axillary dissection for axillary staging in patients with early stage breast cancer. Ann Surg Oncol 2004; 11: 846–53.

[111] Zorzuma G, Garcia-Velloso MJ, Sola J, Regueira FM, Pina L, Beorlegui C. 18F–FDG PET complemented with sentinel lymph node biopsy in the detection of axillary involvement in breast cancer. Eur J Surg Oncol 2004; 30: 15–9.

[112] Breslin TM, Cohen L, Sahin A et al. Sentinel lymph node biopsy is accurate after neoadjuvant chemotherapy for breast cancer. J Clin Oncol 2000; 18: 3480–6.

[113] Fernandez A, Cortes M, Benito E et al. Gamma probe sentinel node localization and biopsy in breast cancer patients treated with a neoadjuvant chemotherapy scheme. Nucl Med Commun 2001; 22: 361–6.

[114] Haid A, Tausch C, Lang A et al. Is sentinel lymph node biopsy reliable and indicated after preoperative chemotherapy in patients with breast carcinoma? Cancer 2001; 92: 1080–4.

[115] Brady EW. Sentinel lymph node mapping following neoadjuvant chemotherapy for breast cancer. Breast J 2002; 8: 97–100.

[116] Stearns V, Ewing CA, Slack R, Penannen MF, Hayes DF, Tsangaris TN. Sentinel lymphadenectomy after neoadjuvant chemotherapy for breast cancer may reliably represent the axilla except for inflammatory breast cancer. Ann Surg Oncol 2002; 9: 235–42.

[117] Miller AR, Thomasen VE, Yeh IT et al. Analysis of sentinel lymph node mapping with immediate pathologic review in patients receiving preoperative chemotherapy for breast carcinoma. Ann Surg Oncol 2002; 9: 243–7.

[118] Julian TB, Dusi D, Wolmark N. Sentinel node biopsy after neoadjuvant chemotherapy for breast cancer. Am J Surg 2002; 184: 315–7.

[119] Piato JR, Barros AC, Pincerato KM, Sampaio AP, Pinotti JA. Sentinel lymph node biopsy in breast cancer after neoadjuvant chemotherapy. A pilot study. Eur J Surg Oncol 2003; 29: 118–20.

[120] Patel NA, Piper G, Patel JA, Malay MB, Julian TB. Accurate axillary nodal staging can be achieved after neoadjuvant therapy for locally advanced breast cancer. Am Surg 2004; 70: 696–9; discussion 699–700.

[121] Mamounas EP, Brown A, Anderson S et al. Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2005; 23: 2694–702.