

Blue dye is sufficient for sentinel lymph node biopsy in breast cancer

C. H. Ang, M. Y. Tan, C. Teo, D. W. Seah, J. C. Chen, M. Y. P. Chan and E. Y. Tan

Department of General Surgery, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore

Correspondence to: Dr E. Y. Tan (e-mail: ern_yu_tan@ttsh.com.sg)

Background: Most previous studies have reported superior results when blue dye and radiocolloids were used together for sentinel lymph node (SLN) biopsy in early breast cancer. Blue dye was reported to perform poorly when used alone, although more recent studies have found otherwise. This study reviewed the authors' practice of performing SLN biopsy with blue dye alone.

Methods: This was a retrospective review of patients who underwent SLN biopsy using blue dye alone from 2001 to 2005, when SLN biopsy was performed selectively and always followed by axillary lymph node dissection (ALND), and from 2006 to 2010, when SLN biopsy was offered to all suitable patients and ALND done only when the SLN was not identified or positive for metastasis.

Results: Between 2001 and 2005, 170 patients underwent SLN biopsy with blue dye alone. The overall SLN non-identification rate was 8.4 per cent. The overall false-negative rate was 34 per cent, but decreased with each subsequent year to 13 per cent in 2005. From 2006 to 2010, 610 patients underwent SLN biopsy with blue dye alone. The SLN was not identified in 12 patients (2.0 per cent) and no significant contributing factor was identified. A median of 2 (range 1–11) SLNs were identified. A non-SLN was found to be positive for metastasis in two patients with negative SLNs. Axillary nodal recurrence developed in one patient; none developed internal mammary nodal recurrence. Anaphylaxis occurred in one patient.

Conclusion: Blue dye performed well as a single modality for SLN biopsy. Non-identification, axillary nodal recurrence and serious allergic reactions were uncommon.

Paper accepted 1 November 2013

Published online 3 February 2014 in Wiley Online Library (www.bjs.co.uk). DOI: 10.1002/bjs.9390

Introduction

Sentinel lymph node (SLN) biopsy has replaced full axillary lymph node dissection (ALND) as the standard of care for T1 and T2 breast tumours without clinically involved nodes after large trials demonstrated comparable clinical benefit and reduced arm morbidity^{1–6}. As the SLN is the first node to be affected by sequential directional tumour spread from the breast, it is representative of the status of the entire axillary nodal basin; it is therefore imperative that the sentinel node is identified accurately. Blue dyes and radiocolloid tracers have been used, either alone or in combination, to identify the SLN for surgical excision^{7–9}. These dyes and tracers are designed to drain efficiently and quickly from the site of injection in the breast, and to be retained within the first-tier (low level I) nodes long enough for the SLN to be identified during surgery. This has important clinical implications. Because the particles continue to diffuse through the axillary

nodal levels over time, a 'blue' or 'hot' node may not necessarily represent the SLN, but instead a second- or even third-tier, non-sentinel node. Furthermore, there are no specific anatomical landmarks or histological features that can distinguish a true SLN from a non-sentinel node. Therefore, a false-negative result can potentially occur should a node other than the true sentinel node be identified.

Most of the large trials from which the feasibility and safety of SLN biopsy were established used a combination of blue dye and radiocolloid. Dual modalities were reported to be superior to a single method in terms of lower non-identification and false-negative rates^{10–13}. However, with improvements in radioisotope imaging and shielding, greater familiarity with the technique and absence of serious allergic reactions typical of those seen with blue dyes, many authors began to advocate the sole use of radiocolloids¹⁴. Initial studies reported that blue dye

alone performed poorly without the concomitant use of radiocolloids, but results comparable with dual-modality SLN biopsy have been documented more recently^{15,16}. Serious allergic reactions were reported to be rare.

The use of blue dye alone remains a popular option because of its technical simplicity and because it does not require any additional equipment or procedures. At the authors' institution, blue dye alone is used in the majority of patients. This was initially due to the lack of in-house radioisotope imaging facilities but, with increasing experience, surgeons have become highly proficient at using blue dye as a single modality and it is now standard practice. The present study reviewed the results of SLN biopsy at the authors' institute over 10 years. From 2001 to 2005, SLN biopsy was done selectively and always followed by ALND. From 2006 to 2010, all suitable patients underwent SLN biopsy, and ALND was carried out only when the SLN was not identified or positive for metastasis. The non-identification rate of the SLN, locoregional recurrence and allergic reactions to the blue dye were evaluated.

Methods

This retrospective review of patients who underwent SLN biopsy at the authors' institute between 2001 and 2010 had ethics committee approval. In the interval 2001–2005, SLN biopsies were carried out selectively, according to surgeon preference, and were always followed by ALND at the same operation. During this interval, up to five surgeons performed SLN biopsy. However, by 2004 the SLN biopsies were done mainly by a single surgeon, who had been performing the procedure since 2001.

Between 2006 and 2010, all suitable patients underwent SLN biopsy, and ALND was performed only when the SLN was not identified or was involved by metastasis. This included all eligible patients with invasive breast tumours less than 5 cm in diameter, with no clinically palpable axillary nodes, and those in whom a biopsy of sonographically enlarged nodes proved negative for malignancy. Patients with ductal carcinoma *in situ* (DCIS) were offered SLN biopsy if undergoing mastectomy, and in selected cases if undergoing wide local excision, according to surgeon preference. SLN biopsy was performed by one of four accredited breast surgeons.

Sentinel lymph node procedure

When blue dye alone was used, 2 ml undiluted Patent V™ blue dye (Aspen Pharmacare, St Leonards, New South

Wales, Australia) was injected into the subareolar plexus with the patient under general anaesthesia, followed by 5 min of manual massage. SLNs were identified as blue-coloured level I nodes with blue lymphatic channels leading up to them. Methylene blue dye was used in patients with a documented allergy to sulphur drugs. When radiocolloid was used, 2 ml technetium-99 was injected peritumorally followed by lymphoscintigraphy approximately 2 h later to map radioactive tracer uptake in the nodal basins. SLNs were then identified with a hand-held γ counter during surgery. The SLNs were sent for intraoperative frozen-section analysis, routinely in those with histological confirmation of invasive breast cancer and selectively in those with DCIS.

Histology

Excess adipose tissue surrounding the nodes was removed and each SLN sliced serially at 2–3-mm intervals. The entire node was then snap-frozen in liquid nitrogen and placed in frozen-section embedding medium on a cryostat object disc. Each slice was further sectioned at intervals of 40 μ m to obtain three sections that were stained in haematoxylin and eosin and then examined using routine light microscopy. The presence or absence of tumour deposits was recorded according to current cancer reporting guidelines provided by the College of American Pathologists (October 2009)¹⁷. The SLN was considered positive when tumour deposits larger than 0.2 mm were present, and negative when no tumour cells were detected or only single tumour cells or tumour cell clusters no larger than 0.2 mm (isolated tumour cells) were present. Subsequently, the entire SLN was formalin-fixed and paraffin-embedded to obtain permanent sections for final analysis, where an additional one to six levels of each slice of the node were examined. Immunohistochemistry was carried out only when confirmation of microscopic tumour deposits was needed.

Statistical analysis

The rate of false-negative SLN biopsy was calculated as $(FN/FN + TP) \times 100$, where FN is the number of false negatives and TP the number of true positives.

Associations between a false-negative SLN result and standard clinicopathological parameters, including patient age, tumour size, histology, tumour grade, lymphovascular invasion, and oestrogen and progesterone receptor status, were investigated. Analyses were performed using Mann–Whitney *U* test for age and tumour size, the χ^2 test for trend for tumour grade, and the χ^2 test

Table 1 Details of sentinel lymph node biopsy performed with blue dye alone from 2001 to 2005 (154 patients), and from 2006 to 2010 (598 patients)

Year	SLN-positive	SLN-negative	Axillary node-positive	Axillary node-negative	False-negative rate (%)†	Accuracy (%)
2001	6	16	11	11	45	77
2002	19	56	31	44	39	84
2003	2	16	3	15	33	94
2004	3	17	3	17	0	100
2005	7	12	8	11	13	95
2006	5	51				
2007	22	94*				
2008	38	98				
2009	30	111*				
2010	32	117				

*In both 2007 and 2009 there was one patient in whom the sentinel lymph node (SLN) was negative, but a non-SLN in the axillary tail of the mastectomy specimen was positive for metastasis. †False-negative rate was calculated as $(FN/FN + TP) \times 100$, where FN is the number of false negatives and TP the number of true positives.

for other categorical variables. Fisher's exact test was used to compare the incidence of nodal recurrence between the two time intervals. A two-tailed *P* value was calculated in all analyses, and $P < 0.050$ was considered statistically significant. All univariable analyses were done using GraphPad Prism® version 4 (GraphPad, San Diego, California, USA).

Results

First interval (2001–2005)

Between 2001 and 2005, 191 patients underwent SLNB, followed by ALND. Blue dye alone was used in 170 patients (89.0 per cent), radiocolloid alone in seven patients (3.7 per cent) and a combination of both blue dye and radiocolloid in the remaining 14 (7.3 per cent). Some 86 of 191 SLN biopsies were performed together with a mastectomy and 105 with a wide local excision. The median age of the patients was 53 (range 24–84) years. The majority of tumours were classified as invasive ductal carcinoma of no special subtype (157 of 191, 82.2 per cent); nine were classified as mucinous carcinoma, three as medullary carcinoma, two as papillary carcinoma, one as cribriform carcinoma, one as tubular carcinoma, ten as DCIS and eight as invasive lobular carcinoma. Median follow-up was 120 (range 96–144) months.

The overall SLN non-identification rate was 8.4 per cent (16 of 191). All 16 instances occurred among the 170 patients in whom blue dye alone was used. The non-identification for this group was therefore 9.4 per cent (16 of 170). The overall false-negative rate was 31 per cent (21 of 68).

Among the 154 patients in whom SLNs were found, the median number identified was 1 (range 1–10), with a mean(s.d.) of 2.0(1.7). A single SLN was identified in

Table 2 Associations between clinicopathological factors and sentinel lymph node biopsy result among 56 patients with confirmed nodal metastasis between 2001 and 2005

	False-negative SLN (n = 19)	True-positive SLN (n = 37)	<i>P</i> †
Age (years)*	52 (35–72)	49 (33–77)	0.322‡
Tumour size (mm)*	24 (3–40)	24.5 (1–45)	0.240‡
Tumour histology			1.000§
Invasive ductal carcinoma	18	35	
Invasive lobular carcinoma	1	2	
Tumour grade			0.211¶
1	3	2	
2	10	19	
3	6	16	
Lymphovascular invasion			0.183
Yes	16	25	
No	3	12	
Oestrogen receptor status			0.278
Positive	15	24	
Negative	4	13	
Progesterone receptor status			0.400
Positive	12	19	
Negative	7	18	

*Values are median (range). SLN, sentinel lymph node. † χ^2 test, except ‡Mann–Whitney *U* test, §Fisher's exact test and ¶ χ^2 test for trend.

81 (52.6 per cent) of 154 patients. Nodal metastasis was confirmed on final analysis in 56 patients (FN + TP), but missed in the SLN in 19 patients (FN), giving a false-negative rate of 34 per cent (Table 1). The false-negative rate decreased with each year, reaching 13 per cent in 2005. False-negative SLN results also occurred among those who underwent SLN biopsy with radiocolloid. The SLN was falsely negative in one patient in whom radiocolloid alone was used, and in one patient in whom both techniques were used. A false-negative SLN result was not associated with any clinicopathological factor (Table 2).

Second interval (2006–2010)

Between 2006 and 2010, 614 patients underwent SLN biopsy. Blue dye alone was used in 610 patients (99.3 per cent), radiocolloid in two and both methods in the remaining two patients. Of the 614 patients, 316 underwent SLN biopsy together with a mastectomy and 298 with a wide local excision. The median age was 54 (range 24–79) years. Again, the majority of tumours were invasive ductal carcinoma of no special type (434 of 614, 70.7 per cent). The rest of the tumours were classified histologically as mucinous carcinoma (17), tubular carcinoma (10), cribriform carcinoma (4), metaplastic carcinoma (3), neuroendocrine carcinoma (3), papillary carcinoma (3), adenoid cystic carcinoma (1), medullary carcinoma (1), DCIS (103) and invasive lobular carcinoma (35). Median follow-up was 60 (range 36–84) months.

Analysis was based on the 610 patients in whom blue dye alone was used. The SLN was identified in 598 of 610 patients (non-identification rate 2.0 per cent). The median number of SLNs identified was 2 (range 1–11), with a mean(s.d.) of 2.5(2.1). A single SLN was identified in 227 (38.0 per cent) of 598 patients.

The SLN was not identified in just 12 patients, of whom only one had involved axillary nodes. On review of the preoperative breast ultrasound examination, two small axillary nodes with thickened cortices but preserved fatty hilum were noted, possibly suggesting nodal involvement. Two patients had been operated on previously: one had undergone wide local excision of a tumour in the upper outer quadrant, and another had had multiple previous incision and drainage procedures for hidradenitis suppurativa of the ipsilateral axilla. No other factors that could have contributed to failure to identify the SLN were identified among the remaining ten patients. Two tumours were located medially and one was retroareolar, and 11 of 12 were invasive ductal carcinomas. The cases of non-identification did not occur more frequently with a particular surgeon.

Metastatic disease was identified in the SLN in 128 (21.4 per cent) of 598 patients, with micrometastatic deposits present in 11 of these. Of the 470 patients with a negative SLN, metastasis was found in a non-sentinel node present in the axillary tail of the mastectomy specimen in two patients. One of these patients had a 15-mm grade 3 invasive ductal carcinoma (not otherwise specified); two SLNs had been identified and both were negative for malignancy. The other patient had a 45-mm grade 3 invasive ductal carcinoma (not otherwise specified); four SLNs had been identified and all were negative for malignancy.

Breast cancer recurrence

During the later interval ALND was not performed in patients with a negative SLN. Ipsilateral axillary nodal recurrence was subsequently diagnosed in one patient, four patients developed local (chest wall or ipsilateral breast) recurrence, and two developed distant recurrence without locoregional recurrence. No patient developed recurrent disease in the internal mammary nodes (IMNs). During the early interval, one patient developed axillary nodal recurrence, three patients developed local recurrence in the chest wall or ipsilateral breast, and four patients developed distant recurrence without locoregional recurrence. The incidence of nodal recurrence was similar in both intervals ($P = 0.351$), even though all patients with a negative SLN underwent ALND during the early period.

Allergic reactions

Over the 10 years, allergic reactions to the blue dye were rare. Two patients developed urticaria during the course of the operation but were otherwise haemodynamically stable and surgery proceeded uneventfully. One patient developed anaphylaxis, and surgery had to be discontinued for resuscitation.

Discussion

Early trials mostly used both blue dye and radiocolloid imaging for SLN biopsy, and most studies have reported a non-identification rate of less than 5 per cent and a false-negative rate below 10 per cent^{3,5,18,19}. Use of blue dye and radiocolloid imaging complement each other. Blue dye colours the SLN and aids identification but, as the dye is not visible through tissue, successful identification requires adequate exposure along the correct tissue planes. In contrast, the radiocolloid signal can penetrate tissue layers. Bleeding further interferes with visualization of the blue dye. Identification of the SLN using blue dye alone is therefore highly dependent on surgeon experience and familiarity with the technique.

With increasing experience, more surgeons have become comfortable with using a single SLN identification technique. Many prefer radiocolloid because of the high rate of successful SLN identification, low false-negative rates and negligible risk of serious allergic reactions. Randomized trials comparing blue dye alone with combined dye and radiocolloid mapping seemed to suggest little advantage of adding blue dye to radiocolloid²⁰. One study¹¹ reported higher SLN false-negative rates and another²¹ reported lower identification rates with blue dye alone. However, enthusiasm for use of blue dye persists,

primarily because no special equipment or procedures are necessary. Although the amount of radioactivity is considered too low to mandate shielding, institutes still require proper licensing, accreditation and protocols for the handling, storage and disposal of radiocolloids. On the other hand, blue dyes require no specific protocols and can be administered by the surgeon.

Although earlier studies^{12,22,23} found dual modalities to be superior in terms of lower non-identification and false-negative rates, more recent studies^{15,16} have reported comparable results with blue dye alone, suggesting that results improve with familiarity and experience. This trend was reflected in the present study. The false-negative rate in the initial years was high, particularly in 2002, when up to five surgeons were starting to perform SLN biopsy. The false-negative rate decreased with each subsequent year, and was markedly lower by 2004 and 2005, when mainly a single surgeon, who had been performing SLN biopsy since 2001, was carrying out the biopsies. Increasing surgeon experience was the most likely contributor to this decrease in false-negative rate, a postulate strengthened by the lack of any association of a false-negative SLN result with standard clinicopathological factors.

In the authors' institute, blue dye alone is used routinely for SLN biopsy. Initially, this was because of a lack of in-house nuclear medicine facilities to support radiocolloid administration and lymphoscintigraphy. However, even once these were available, radiocolloid was seldom used because of the additional logistics involved. Patients had to be admitted several hours before the procedure for radiocolloid injection and lymphoscintigraphy, and to be transported between multiple sites. Furthermore, the non-identification rate of 2.0 per cent with blue dye alone does not justify the additional procedures and costs incurred with radiocolloid use. The findings also suggest that it would be difficult to adopt a more selective approach given that no preoperative predictors of failure to identify the SLN could be identified. Tumours located medially can preferentially drain to the IMNs instead of the axillary nodes; however, lateral tumours were more common among the 12 patients in whom the SLN was not identified. Radiocolloid imaging would also probably have failed in the two patients who had undergone previous surgery as this could have disrupted lymphatic drainage to the axillary nodes. Current institutional protocols do not allow intraoperative radiocolloid administration after the blue dye has failed to identify the SLN.

A further criticism is that fewer SLNs are identified when blue dye alone is used. There is concern that this may increase the likelihood of missing a positive SLN and

producing a false-negative result. There is indirect evidence from some studies^{24,25} that there may be an optimal number of SLNs that should ideally be harvested, given that the ratio of the number of negative SLNs to the total number of SLNs harvested can predict the likelihood of additional non-SLN involvement. There is no consensus on what this optimal number should be. One study²⁶ reported that the positive SLN was removed by the third SLN harvested, implying that there is little benefit in removing more than three SLNs. In the present study, from 2006 onwards, a single SLN was identified in about one-third of patients. The median number of SLNs identified here is similar to that reported by several other studies^{2,4,5,24,26} performed with dual-modality SLN biopsy, suggesting that there is no difference in the number of SLNs identified using either method when performed by experienced surgeons. It can also be inferred from the present findings that there is a low likelihood of a false-negative SLN and residual nodal disease when ALND is omitted. Using axillary nodal recurrence as a surrogate for the false-negative rate, such recurrence was no more common among those who had undergone SLN biopsy with blue dye alone between 2006 and 2010.

Another advantage of radiocolloid lymphoscintigraphy over blue dye is that it facilitates targeted IMN biopsy. Targeted IMN biopsy can be performed with a high success rate, and with minimal risk of pleural breach and internal mammary vascular injury compared with IMN dissection. This has prompted further investigation of the benefit of IMN evaluation as up to 8 per cent of patients with negative axillary nodes reportedly have IMN involvement and are at risk of being undertreated if these are unrecognized^{27–29}. Although additional information from IMN evaluation has changed treatment recommendations in some patients initially thought to be node-negative, this is mostly likely limited to a small minority of patients^{28,30,31}. At the authors' institute, patients with negative axillary nodes deemed to be at high risk of recurrence are still recommended to undergo systemic chemotherapy according to treatment guidelines, and radiation fields cover the IMNs for all medial tumours, which are those most likely to drain to the IMN³². This means that many patients with possible IMN metastasis already receive adequate treatment even without documented IMN involvement. Interestingly, all three patients in the present series who developed IMN recurrence in the interval from 2006 to 2010, when SLN biopsy was the standard of care, had presented with clinically involved axillary nodes and had undergone ALND without previous SLN biopsy, and all had received systemic chemotherapy and radiotherapy. Distant disease was detected concurrently in all patients, suggesting that

the IMN recurrence was part of a systemic relapse rather than a mere failure to treat unrecognized IMN disease.

This study has shown that SLN biopsy with blue dye alone performs well in experienced hands and is rarely associated with serious allergic reactions. Radiocolloid imaging is not expected to reduce non-identification rates significantly, nor is it expected to change treatment recommendations in most instances, even with the added advantage of IMN evaluation. Its technical simplicity without the need for special equipment, specially trained personnel or additional logistic planning, or the need for radioactivity licensing and monitoring, makes SLN biopsy with blue dye particularly applicable to centres that do not have in-house nuclear medicine facilities.

Disclosure

The authors declare no conflict of interest.

References

- Straver M, Meijnen P, van Tienhoven G, van de Velde CJ, Mansel RE, Bogaerts J *et al.* Sentinel node identification rate and nodal involvement in the EORTC 10981-22023 AMAROS trial. *Ann Surg Oncol* 2010; **17**: 1854–1861.
- Ashikaga T, Krag DN, Land SR, Julian TB, Anderson SJ, Brown AM *et al.* Morbidity results from the NSABP B-32 trial comparing sentinel lymph node dissection *versus* axillary dissection. *J Surg Oncol* 2010; **102**: 111–118.
- Krag D, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP *et al.* Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol* 2010; **11**: 927–933.
- Krag D, Anderson SJ, Julian TB, Brown AM, Harlow SP, Ashikaga T *et al.* Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. *Lancet Oncol* 2007; **8**: 881–888.
- Gill G; SNAC Trial Group of the Royal Australasian College of Surgeons (RACS) and NHMRC Clinical Trials Centre. Sentinel-lymph-node-based management or routine axillary clearance? One-year outcomes of sentinel node biopsy *versus* axillary clearance (SNAC): a randomized controlled surgical trial. *Ann Surg Oncol* 2009; **16**: 266–275.
- Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM *et al.* Randomized multicenter trial of sentinel node biopsy *versus* standard axillary treatment in operable breast cancer: the ALMANAC Trial. *J Natl Cancer Inst* 2006; **98**: 599–609.
- Giuliano A, Kirgan D, Guenther J, Morton D. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994; **220**: 391–398.
- Giuliano A, Jones R, Brennan M, Statman R. Sentinel lymphadenectomy in breast cancer. *J Clin Oncol* 1997; **15**: 2345–2350.
- Albertini J, Lyman G, Cox C, Yeatman T, Balducci L, Ku N *et al.* Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. *JAMA* 1996; **276**: 1818–1822.
- Schirrmeyer H, Kotzerke J, Vogl F, Buck A, Czech N, Koretz K *et al.* Prospective evaluation of factors influencing success rates of sentinel node biopsy in 814 breast cancer patients. *Cancer Biother Radiopharm* 2004; **19**: 784–790.
- Syme DB, Collins JP, Mann GB. Comparison of blue dye and isotope with blue dye alone in breast sentinel node biopsy. *ANZ J Surg* 2005; **75**: 817–821.
- Cody H III. Clinical aspects of sentinel node biopsy. *Breast Cancer Res* 2001; **3**: 104–108.
- Goyal A, Newcombe RG, Chhabra A, Mansel RE; ALMANAC Trialists Group. Factors affecting failed localisation and false-negative rates of sentinel node biopsy in breast cancer – results of the ALMANAC validation phase. *Breast Cancer Res Treat* 2006; **99**: 203–208.
- Hayashida T, Jinno H, Sakata M, Takahashi M, Onishi T, Seki H *et al.* Superiority of radioisotope over blue dye for sentinel lymph node detection in breast cancer. *Eur Surg Res* 2010; **44**: 111–116.
- Chintamani, Tandon M, Mishra A, Agarwal U, Saxena S. Sentinel lymph node biopsy using dye alone method is reliable and accurate even after neo-adjuvant chemotherapy in locally advanced breast cancer – a prospective study. *World J Surg Oncol* 2011; **9**: 19.
- Krikanova M, Biggar M, Moss D, Poole G. Accuracy of sentinel node biopsy for breast cancer using blue dye alone. *Breast J* 2010; **16**: 384–388.
- Lester SC, Bose S, Chen YY, Connolly JL, de Baca ME, Fitzgibbons PL *et al.*; Members of the Cancer Committee, College of American Pathologists. Protocol for the examination of specimens from patients with invasive carcinoma of the breast. *Arch Pathol Lab Med* 2009; **133**: 1515–1538.
- Lyman GH, Giuliano AE, Somerfield MR, Benson AB III, Bodurka DC, Burstein HJ *et al.*; American Society of Clinical Oncology. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. *J Clin Oncol* 2005; **23**: 7703–7720.
- Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a metaanalysis. *Cancer* 2006; **106**: 4–16.
- Derossis AM, Fey J, Yeung H, Yeh SD, Heerdt AS, Petrek J *et al.* A trend analysis of the relative value of blue dye and isotope localization in 2000 consecutive cases of sentinel node biopsy for breast cancer. *J Am Coll Surg* 2001; **193**: 473–478.
- Hung WK, Chan CM, Ying M, Chong SF, Mak KL, Yip AW. Randomized clinical trial comparing blue dye with combined dye and isotope for sentinel lymph node biopsy in breast cancer. *Br J Surg* 2005; **92**: 1494–1497.

- 22 Morrow M, Rademaker AW, Bethke KP, Talamonti MS, Dawes LG, Clauson J *et al.* Learning sentinel node biopsy: results of a prospective randomized trial of two techniques. *Surgery* 1999; **126**: 714–720.
- 23 Cserni G, Rajtár M, Boross G, Sinkó M, Svébis M, Baltás 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**: 592–597.
- 24 Barranger E, Coutant C, Flahault A, Delpech Y, Darai E, Uzan S. An axilla scoring system to predict non-sentinel lymph node status in breast cancer patients with sentinel lymph node involvement. *Breast Cancer Res Treat* 2005; **91**: 113–119.
- 25 Tan EY, Ho B, Chen JJ, Ho PW, Teo C, Earnest A *et al.* Predictors of nonsentinel nodal involvement to aid intraoperative decision making in breast cancer patients with positive sentinel lymph nodes. *ISRN Oncol* 2011; **2011**: 2011539503.
- 26 Lynch MA, Jackson J, Kim JA, Leeming RA. Optimal number of radioactive sentinel lymph nodes to remove for accurate axillary staging of breast cancer. *Surgery* 2008; **144**: 525–531.
- 27 Park C, Seid P, Morita E, Iwanaga K, Weinberg V, Quivey J *et al.* Internal mammary sentinel lymph node mapping for invasive breast cancer: implications for staging and treatment. *Breast J* 2005; **11**: 29–33.
- 28 Carcoforo P, Sortini D, Feggi L, Feo CV, Soliani G, Panareo S *et al.* Clinical and therapeutic importance of sentinel node biopsy of the internal mammary chain in patients with breast cancer: a single-center study with long-term follow-up. *Ann Surg Oncol* 2006; **13**: 1338–1343.
- 29 Chagpar AB, Kehdy F, Scoggins CR, Martin RC II, Carlson DJ, Laidley AL *et al.* Effect of lymphoscintigraphy drainage patterns on sentinel lymph node biopsy in patients with breast cancer. *Am J Surg* 2005; **190**: 557–562.
- 30 Galimberti V, Veronesi P, Arnone P, De Cicco C, Renne G, Intra M *et al.* Stage migration after biopsy of internal mammary chain lymph nodes in breast cancer patients. *Ann Surg Oncol* 2002; **9**: 924–928.
- 31 Hong J, Choy E, Soni N, Carmalt H, Gillett D, Spillane AJ. Extra-axillary sentinel node biopsy in the management of early breast cancer. *Eur J Surg Oncol* 2005; **31**: 942–948.
- 32 Huang O, Wang L, Shen K, Lin H, Hu Z, Liu G *et al.* Breast cancer subpopulation with high risk of internal mammary lymph nodes metastasis: analysis of 2269 Chinese breast cancer patients treated with extended radical mastectomy. *Breast Cancer Res Treat* 2008; **107**: 379–387.

Editor's commentary

Sentinel lymph node biopsy is the standard of care for staging the axilla in early breast cancer. Using dual markers, radiocolloid tracer and blue dye, the sentinel nodes can be identified reliably with low false-negative rates. Radiocolloid tracer alone is as good as the combination of markers. Blue dye alone, however, is technically more challenging and requires careful dissection. In experienced hands, as here, the sentinel node identification rates are good and false-negative rates are low, but these results may not be generalizable for all settings, especially where there are low procedure volumes and less experienced surgeons.

M. Sund
BJS Editor