Sentinel lymph node biopsy in breast cancer — a learning curve

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The strongest predictor of recurrence versus survival in women with breast cancer is the presence or absence of lymph node metastases.[1] Regional nodal status can be accurately predicted by identification and examination of the sentinel lymph node (SLN). If the SLN shows no evidence of tumour it is over 90% certain that the remaining regional lymph nodes are negative.[2]

The use of sentinel lymph node direction (SLND) in early breast cancer can spare patients with node-negative disease the adverse effects of complete axillary lymph node dissection (ALND). In this study, an initial experience of 30 women with early stage breast cancer and clinically negative nodes who underwent SLN mapping followed by ALND is presented. The success and failure of vital blue dye and lymphoscintigraphic technique to identify the SLN are examined. Features of the breast cancers which can result in false-negative results are discussed. Based on this initial experience with SLN biopsy recommendations are made which may help to shorten the learning curve for this technique.

Patients and methods

Thirty women with early breast cancer and clinically negative nodes (Table I) underwent SLN mapping followed by level I and II completion ALND. Vital blue dye (Patent Blue V, Solulab, Johannesburg) alone and together with radioactive colloid (^{99m}Technetium-nanocolloid) were used to identify the SLN. On the morning of the operation, 26 patients underwent lymphoscintigraphy.

One millicurie of radiocolloid was given by intradermal injection (ID) at the tumour site and into the related subareolar quadrant. The patient was placed under the gamma camera with the arm abducted, the position that is used for axillary dissection. Images acquired included the axilla, breast, internal mammary and supraclavicular regions. The location of the SLN was marked on the skin. The operation was performed in the afternoon. Intra-operatively 4 ml of Patent Blue V (PBV) was injected into the breast parenchyma (intraparenchymal, IP) around the tumour. The injection sites were gently massaged for 10 minutes to promote flow of dye to the axilla.

The axilla was then opened and all nodes stained by the dye were removed. A hand-held gamma probe was used to identify nodes with radioactivity. Any node with 10% or more of the total tumour count was regarded as a 'hot' node and removed. The operation was followed by the appropriate breast surgery (complete or segmental mastectomy) and ALND. The SLN was bisected and evaluated intra-operatively by scraping the cut surface and performing immediate 'scrimp' cytology.[3] All lymph node material was re-examined in the laboratory using haematoxylin and eosin staining. Where necessary, immunocytochemical stains were used to identify micrometastases.

TABLE I. CHARACTERISTICS OF CANCERS AND LYMPH NODES

Primary tumour	Tumour* number	Axilla positive
Tis		
Tis (Paget's)	**2**	**0**
T_1		
T_1 mic	**1**	**0**
T_1 A	**1**	**0**
T_1 B	**4**	**2†**
T_1 C	**15**	**2**
T_2	**7**	**4**
Total	**30**	**8**

**AJCC Cancer Staging Manual.* 6th ed. Lippincott Williams and Wilkins, 2002.
†Micrometastasis ≤ 2.0 mm.

Results (Table II)

The SLN was identified in 29 of the 30 patients. No SLN was identified in 1 patient who underwent lymphatic mapping using blue dye only. Thirty patients had blue dye mapping, with 3 failures of SLN identification. Twenty-six patients had radiocolloid mapping, with 1 failure.

Axillary metastases were found in 8 patients (27%). Five patient had macrometastases, identified intra-operatively. One patient had a false-negative SLN. This patient had multifocal cancers with a total dimension of 31 mm — 2 non-SLNs (NSLNs) contained macrometastases. Two patients had micrometastases (≤ 2 mm) in the SLN, detected using haematoxylin and eosin staining of paraffin sections and confirmed by cytokeratin immunohistochemistry.

Of the 5 patients with macrometastases in the SLN, 4 also

TABLE II. RESULTS OF LYMPHATIC MAPPING

Characteristics	*N*	%
Patients with attempted mapping	**30**	**–**
Patients with successful mapping	**29**	
Identification rate	**29/30**	**97**
Isotope SLN success	**25/26**	**96**
Blue dye SLN	**27/30**	**90**
Positive axillary basins	**8**	**20**
Macrometastases	**6**	
Micrometastases	**2**	
False-negative SLN	**1**	

had macrometastases in the NSLNs. Of the 2 patients with micrometastases in the SLN, neither had involvement of the NSLNs.

Discussion

In the study, vital blue dye was successful in 90% of SLN mapping. This is similar to the results of IP dye injection reported by Beitsch *et al.*[4] (94%) and Linehan *et al.*[5] (78%). The 3 cases of dye failure illustrate the problems encountered with this technique. One patient had an excision biopsy before mapping — it is likely that lymphatic flow was partly interrupted after surgery and insufficient time may have been allowed for dye to reach the axilla. The patient with a false-negative SLN illustrates the value of excising all blue nodes including nodes only faintly coloured by dye; lymph nodes with metastases may take up less dye than normal nodes and therefore be less obvious than the second tier of lymph nodes.

In the third and final case of dye failure the patient had had a reduction mammoplasty. This may have altered parenchymal lymphatic flow. Where the nipple-areolar complex is separated from underlying parenchyma, subareolar dye injection is also likely to be affected. So in patients who have undergone cosmetic surgery, ID injection of dye into the skin of the affected quadrant is the preferred technique.

ID injection of radiotracer over the tumour and the related subareolar quadrant resulted in SLN identification using the intraoperative gamma probe[2] in 25 of the 26 cases (96%). In most patients the dermal and parenchymal lymphatics of the breast drain to the same SLN.[6] However, a non-randomised study comparing ID with IP isotope injection[6] showed that ID isotope was the most successful in SLN mapping. After ID injection, the SLN contains 5 times more radioactivity than after IP radiocolloid so that the SLN is then easier to locate with the intraoperative gamma probe. Where the IP site is used for upper quadrant tumours, background radiation or 'shine-through' from the injection route can make identification of the axillary SLN difficult. But using the ID route the radioactivity in the skin can be retracted away from the axilla. It is then easier to locate the SLNs with the gamma probe.[6] The only case where the SLN was not found with the intraoperative probe had a lower inner quadrant cancer. An axillary SLN was marked at pre-operative lymphoscintigraphy and located using blue dye injection. Why the probe failed is not certain, but this case highlights the value of a dual technique for SLN mapping.

In the current study, the SLN was falsely negative in 1 patient with multi-focal cancers to a total dimension of 31 mm. Boolbol *et al.*[7] have shown that the false-negative rate increases with the size of the cancer. In a prospective study of over 2 000 patients, Martin *et al.*[8] demonstrated that the accuracy of SLN biopsy is related to the number of SLNs removed, and they advocated removal of all 'hot' and blue nodes. While blue dye may salvage cases in which isotope fails to identify the SLN, Wong *et al.*[9] showed that greater numbers of SLNs are located with radiocolloid than with blue dye, and in their study of 1 436 patients having SLN biopsies, the false-negative rate was significantly higher in those patients who had only 1 SLN removed compared with those who had multiple SLN identified. The result of the University of Louisville breast cancer sentinel node study[10] and the meta-analysis of 11 blue-dye series reported by Cody[11] confirm that false-negative results with blue dye are twice as frequent as with isotope. It is therefore important in cases where difficulty with SLN mapping can be expected (large tumours, multifocal cancers, previous breast surgery) to use a dual mapping technique. Both radiocolloid and blue dye should be given by ID injection and all sentinel nodes should be removed.

Most macrometastates are easily detected using intraoperative scrimp cytology. The other axillary nodes must be removed as the risk of NSLN involvement is greater than 50%.[12] Five of the 6 patients with SLN macrometastases in this small study had involvement of the NSLNs.

The 2 patients with micrometastases in the SLN had no metastatic disease in the NSLNs. Micrometastases (< 2 mm) can easily be overlooked on gross examination and may not be sampled cytologically at operation. In the studies reported by Chu *et al.*,[12,13] SLN micrometastases were associated with a risk of NSLN involvement of less than 10%. The delayed diagnosis of micrometastases in the SLN does not require additional surgery to the axilla.[14]

The clinical and prognostic significance of micrometastases is debated.[14] In the author's practice, adjuvant therapy is given for metastatic lymph node involvement irrespective of the size of the metastasis.

Conclusion

Radio-isotope and blue dye should be given by ID injection into the related subareolar quadrant. An ID injection into the skin adjacent to the tumour can be used if there has been previous cosmetic surgery involving the nipple-areolar complex.

Biopsies of the SLNs should continue until all 'blue' and 'hot' nodes are removed. Dual-agent mapping improves the ability to detect multiple SLNs and reduces the false-negative rate associated with use of blue dye alone.

Thanks to Gritzman, Thatcher, Wium and Associates Anatomical Pathologists for the cytological and histopathological examination and to Mrs Rina Genade for typing this manuscript.

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