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## **Intra-operative examination of the sentinel node in breast cancer**

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### **Abstract**

Intra-operative sentinel node analysis allows immediate progression to axillary clearance in patients with node positive breast cancer and reduces the need for re-operation. Despite this, intra-operative sentinel node analysis is infrequently performed in Ireland. We report our experience using this technique. Sentinel node biopsy was performed in 47 consecutive patients with symptomatic T1-T2 clinically node negative breast cancer. Sentinel nodes were examined intra-operatively by frozen section and imprint cytology and definitive histological assessment was performed on paraffin-embedded tissue. The sentinel node was identified in 46 (98%) patients. Twelve patients had axillary metastases. The sensitivity of intra-operative analysis in identifying nodal metastases was 92%. False negative rate was 8%, negative predictive value 97%, and specificity 100%. Intra-operative analysis of the sentinel node allowed re-operation to be avoided in 92% of patients with axillary node metastases. In our experience this technique can be readily introduced with reliable outcomes.

### **Introduction**

The axillary lymph node status is of prognostic and therapeutic importance in patients with breast cancer. Sentinel lymph node biopsy (SNB) is now widely utilised in staging the axilla of patients with T1 – T2 breast cancer. This technique reliably detects lymph node metastases and identifies those patients for whom axillary clearance is necessary<sup>1,2</sup>. Conversely, it allows unnecessary axillary clearance with its attendant morbidity<sup>3</sup> to be avoided in approximately 75% of patients.

Intra-operative assessment of the sentinel node using frozen section or imprint cytology can be used to predict the final histological status of the sentinel node and allow immediate progression to axillary clearance in patients with positive sentinel node<sup>4-8</sup>. Furthermore, patients may be spared the physical and psychological morbidity of re-operation. Despite this, intraoperative lymph node assessment has failed to achieve widespread use in Europe where it is employed in approximately 60% of breast cancer

centres<sup>9</sup>. In Ireland intra-operative lymph node analysis with immediate axillary clearance in node positive cases is rarely used. We report our experience of introducing intra-operative sentinel node analysis to our practice.

## Methods

### *Patients*

The records of forty-seven patients with symptomatic T1 – T2 breast cancer undergoing primary breast cancer surgery and SNB were reviewed.

Individual patient details had been prospectively entered into a breast cancer database. All patients underwent triple-assessment and had a pre-operative diagnosis of breast cancer.

### *Sentinel lymph node mapping*

The sentinel node was identified using a combination of blue dye and radioisotope. Three to 4 hours pre-operatively, 2 mls of Technecium-99-nanocolloid was injected in 4 quadrants around the tumour. One hour pre-operatively 2 mls of 1% lymphazurin blue dye was injected in a similar fashion and lymphatic drainage encouraged by self-massage.

Table 1 Information Present on Patient Reports			
Information	All Contacts n (%)	Telephone n (%)	Visit n (%)
Patient Name	387 (100)	142 (100)	245 (100)
Patient Age/DOB	386 (99.7)	142 (100)	244 (99.6)
Patient Address	384 (99.2)	142 (100)	242 (98.8)
Patient Tel no.	384 (99.2)	141 (99.3)	243 (99.2)
Doctor's name	387 (100)	142 (100)	245 (100)
Presenting Complaint	385 (99.5)	140 (98.6)	245 (100)
Clinical Findings	N/A	N/A	213 (90.3) (N/A=9)
Diagnosis/ Impression	314 (81.9)	92 (66.7) (N/A=4)	222 (90.6)
Management	350 (90.9)	116 (82.9) (N/A=2)	234 (95.5)
Follow up	201 (52.2)	96 (68.6) (N/A=2)	105 (42.9)

### *Operative procedure*

At operation the sentinel lymph node was first located and when feasible approached via the incision planned for resection of the breast tumour. Otherwise a separate incision was made in the axillary skin crease. The sentinel node was located using a hand held gamma probe and/or by direct visualisation of patent blue dye. Once identified the sentinel node (or nodes) was excised and transferred to the histopathology laboratory for analysis by

frozen section and imprint cytology. The surgeon then proceeded to resection of the breast tumour.

#### *Intra-operative sentinel node analysis*

All pathological analysis was performed by a single consultant pathologist (EL). The sentinel node/s were bivalved and touch preparation established from fresh tissue. Smears were analysed by standard H&E techniques. Three sections (5µm) from bivalved nodes were prepared for frozen section using OCT compound (Tissuetek) and freezing spray and samples analysed by H&E staining. Results of the sentinel node analysis were relayed to the operating theatre. In the event of a positive sentinel node, a level 3 axillary clearance was performed.

#### *Definitive lymph node analysis*

The remaining nodal tissue was embedded in paraffin. Approximately six sections from each paraffin embedded lymph node were analysed to determine the final nodal histological status.

### **Results**

The mean patient age was 53 years (range 34-83). Thirty-two patients had ductal carcinoma (68.1%), eight patients (17%) lobular carcinoma, and seven patients (14.9%) mixed tumours. Ten patients (21.3%) underwent mastectomy and 37 patients (78.7%) had wide local excision of the breast tumour. Sentinel lymph node identification was successful in 46 of 47 patients (97.9%). In one patient the sentinel node could not be identified and a level 3 axillary clearance was performed. Final histological analysis identified axillary metastatic disease in twelve patients. Intra-operative assessment of the sentinel node correctly predicted nodal metastatic disease in eleven patients giving a sensitivity of 92% and a negative predictive value of 97%. In one patient intra-operative sentinel node assessment was falsely negative (false negative rate 8%). Intra-operative sentinel node analysis was 100% specific. There were no false positives. Intra-operative examination of the sentinel node allowed 24% of patients to undergo immediate axillary clearance and avoid re-operation.

### **Discussion**

Sentinel node mapping is now an accepted tool in staging the axilla in patients with clinically and radiologically node negative breast cancer. This technique detects axillary nodal metastases with an accuracy of greater than 95%<sup>1,2,10</sup> and allows unnecessary axillary clearance to be avoided in approximately 75% of patients. Furthermore, sentinel node mapping facilitates detection of micrometastases by allowing targeted ultrastaging of a small volume of nodal tissue<sup>11</sup>.

SNB with post-operative histological assessment of the sentinel nodes results in delayed axillary clearance in patients with positive sentinel node. This may lead to increased psychological morbidity for node positive patients and potential delays in initiating adjuvant treatment. From a surgical perspective re-operation on the axilla is technically more demanding than standard axillary clearance. Intra-operative determination of sentinel node status with immediate progression to axillary clearance in the event of metastatic disease may negate these issues.

Intra-operative lymph node analysis relies on accurate assessment and a low false positive rate. Frozen section and imprint cytology are the two most commonly reported techniques. While published reports show great variance in the success of these techniques, sensitivity rates of greater than 90% and false negative rates of less than 10% can be achieved<sup>12</sup>.

In the current study combined frozen section and imprint cytology detected nodal metastatic disease with a sensitivity of 92% and a false negative rate of 8%. Importantly, there were no false positives in this series. Furthermore, intra-operative assessment of the sentinel node allowed immediate decision-making with regard to the requirement for axillary clearance and allowed re-operation to be avoided in approximately one-quarter of our patients. In a review of European practice intra-operative assessment of the sentinel node was performed in 60% of surveyed units<sup>9</sup>. This relatively low figure is surprising given the apparent benefits of this procedure to both patient and surgeon. Guidelines drafted by the European Working Group for Breast Screening Pathology state that intra-operative assessment of axillary sentinel nodes is 'imperative' given that it may allow one-step procedure for patients with positive findings<sup>12</sup>. Use of this technique in Great Britain and Ireland appears to be even lower. This may reflect lack of support in published national guidelines<sup>13</sup> for intra-operative assessment techniques and contrasts with those emanating from the United States of America<sup>14</sup>.

Concerns that have been raised regarding intra-operative sentinel node assessment include perceived prolongation of anaesthesia and operating time, nodal tissue loss during frozen section tissue preparation, the level of expertise required for cytological preparation, and risk of false positive or falsely negative results<sup>15</sup>. While not formally assessed in the current study, it was our experience that by identifying the sentinel node at the beginning of the procedure we were able to perform the tumour resection while node analysis proceeded. Invariably the result from the laboratory coincided with or followed shortly after completion of the breast surgery. In any event, any small delay could be offset against time saved in avoiding re-operation.

These findings are supported by the results of Chicken et al. who found that the report of the intra-operative sentinel node analysis was received prior to completion of the breast surgery in 76% of cases and this occurred despite the requirement for transport of the specimen to an off-site laboratory<sup>16</sup>. Where concerns exist over tissue loss with frozen section, imprint cytology may be employed with similar efficacy without significant loss of nodal tissue however the later technique does require greater expertise in interpretation<sup>14</sup>. High false negative rates have been cited as a further drawback to intra-operative sentinel node analysis<sup>15</sup>. In the current study intraoperative analysis was falsely negative in one patient (8%). This occurred in a patient with 2.1cm grade II lobular carcinoma. This finding is consistent with literature which has shown high false negative rates for frozen section and imprint cytology in the detection of nodal metastases in lobular breast cancer<sup>17</sup>. The availability of appropriate expertise, particularly in the interpretation of cytological preparations appears, however, to be critical in maintaining low false negative rates.

In conclusion, intra-operative assessment of the sentinel node offers significant potential benefits to patients with node positive breast cancer. Nonetheless, this technique remains relatively underemployed. Our early experience shows that intra-operative sentinel node analysis may be readily introduced with reliable outcomes. A combination of touch-imprint cytology and frozen section was found to reliably detect nodal metastases without false positives and to allow re-operation with its potential physiological and psychological side-effects to be avoided.

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**Other References**

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