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One Step Nucleic Acid Amplification (OSNA) positive micrometastases and additional histopathological NSLN metastases: Results from a single institution over 53 months

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ABSTRACT

Introduction: The role of sentinel lymph node micrometastases on histopathological analysis is controversial in axillary staging and management in clinically node negative breast cancer. Long-term studies addressing the clinical relevance of occult breast cancer in sentinel lymph nodes based on molecular analysis are lacking. One Step Nucleic Acid Amplification (OSNA), a highly sensitive assay of cytokeratin 19 mRNA, is used intra-operatively for the detection of lymph node macro- and micrometastases in breast cancer.
Aim: The aim of this study is to review the rate of micrometastases and further histopathological NSLN metastases, in our unit following the introduction of OSNA in Guildford.
Methods: Data was collected prospectively from the period of introduction 01/12/2008 to 31/05/2013. All patients eligible for sentinel lymph node biopsy were offered OSNA and operations were performed by the consultant breast surgeons. Presence or absence of micrometastases depends on the agreed cut-off point on the amplification curve. On detection of micrometastases (+) and positive but inhibited (i+) metastases, a level 1 axillary clearance (ANC) was performed and for a macrometastasis (++), a level 3 ANC was carried out.
Results: 66% of the patients had negative SLN ($n = 672$) and 34% ($n = 336$) had positive sentinel lymph nodes who had further axillary surgery. Of these, 45% ($n = 152/336$) had macrometastases, 40% ($n = 136/336$) had micrometastases and 15% (48/336) had positive but inhibited results. There was no difference in the patient demographics and tumour characteristics in the various positive SLN groups. In patients with micrometastases, 15% (20/136) had further positive NLSNs and a further 6% (8/136) had >4 overall positive nodes (SLN + NSLN) thus requiring adjuvant supraclavicular/chest wall radiotherapy ($p < 0.05$). 25% of node positive patients had further NLSN metastases (85/336) and in these patients, the ratio of positive SLN/harvested SLN (+SLN/SLN) is constant at 1:1. This shows the likelihood of further positive NSLNs if all the harvested lymph nodes are positive. This linear trend is present in both micro-and macrometastases, thus correlating with the size and number of NSLN metastases.

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Conclusion: Our study reflects the tumour burden of NSLNs based on the molecular analysis of the SLN. OSNA has the potential to accurately identify axillary micrometastases. Micrometastases are important as some of the patients with micrometastases had overall four positive nodes [SLN + NSLN] (criteria for radiotherapy in the absence of other adverse clinicopathological features). Also, our study highlights certain factors that predict the NSLN metastases, pending validation by further prospective long-term data. This will allow accurate calculation of the axillary tumour burden, particularly in patients with micrometastases.

Abbreviations

ANC	axillary node clearance
ALND	axillary lymph node dissection
CK19	Cytokeratin 19
DCIS	ductal carcinoma in situ
IDC	invasive ductal carcinoma
ILC	invasive lobular carcinoma
LVI	lymphovascular invasion
mRNA	messenger ribonucleic acid
NSLN	non-sentinel lymph node
OSNA	one step nucleic acid amplification
OS	overall survival
PCR	polymerase chain reaction
SLN	sentinel lymph node
SNB	sentinel node biopsy
WLE	wide local excision
+SLN/SLN	ratio of positive SLN to harvested SLN

Introduction

Sentinel lymph node biopsy has become a widely accepted procedure for axillary staging in clinically node negative breast cancer patients. However, the clinical significance and management of micrometastases on histopathological analysis of the sentinel lymph node is controversial.[1–5] Recent large patient cohort studies with longer follow-up have shown differential prognostic implications for micrometastatic disease in the sentinel lymph node.[6] As their results account for a particular method of SLN analysis, these data may not be applicable to all centres due to the variability in the method of the histopathological sentinel nodal analysis across different units.[1]

Recently, there is considerable interest in intra-operative molecular analysis of the sentinel lymph node by RT-LAMP due to its accuracy and applicability.[7,8] One Step Nucleic Acid Amplification (OSNA) is a highly sensitive, automated and rapid assay that analyses lymph nodes for metastases by detection and amplification of the mRNA of cytokeratin 19 (CK19), an epithelial marker in breast cancer cells.[9] This technique potentially represents the accurate reflection of tumour burden, particularly those with micrometastatic disease who are unlikely to have histopathologically and/or immunohistochemically positive non-sentinel nodes after axillary lymph node dissection (ALND). ALND in these patients may only serve for staging rather than therapeutic purpose and therefore long-term data are needed to address the clinical relevance of molecular biological occult breast cancer in sentinel lymph nodes. Our unit has established the accuracy and histopathological concordance of OSNA in four, high volume, breast cancer centres[10] and has adopted it in routine clinical practice since December 2008. As the first UK centre to introduce OSNA, we have reported the preliminary review of our data on SLN analysis by OSNA.[49] In this study, we describe the rate of NSLN metastases for patients with molecular biological micrometastatic disease in the SLN and compare it with the patients with SLN macrometastatic disease.

Methods

Data were collected prospectively from introduction 01/12/2008 to 31/05/2013. Details of methods have been described elsewhere.[49] All eligible patients were offered OSNA and none declined. All patients had clinically, sonographically and cytologically negative axillae.

Results

A total of 1008 patients had 2151 SLNs analysed with an average of two nodes per patient. 66% of the patients had negative SLN ($n = 672$) and 34% ($n = 336$) had positive sentinel nodes who had further axillary surgery. Of these, 45% ($n = 152/336$) had macrometastases, 40% ($n = 136/336$) had micrometastases and 15% ($n = 48/336$) had positive but inhibited results (now adjusted to a quantifiable result[49]). These results are similar to those reported previously.[49] In addition, 8% (83/1008) of our patients had neo-adjuvant chemotherapy.

Table 1 shows the further breakdown of this additional data. In patients with macrometastases, 38% (57/152) had further positive NSLN and a quarter of these (40/152, 26%) had ≥4 overall nodes. 15% (20/136) of the patients with micrometastases had positive NSLNs. 6% (8/136) had ≥4 overall