Is there a requirement for axillary lymph node dissection following identification of micro-metastasis or isolated tumour cells at sentinel node biopsy for breast cancer?

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ABSTRACT

Introduction: Recent decades have seen a significant shift towards conservative management of the axilla. Increasingly, immunohistochemical analysis of sentinel nodes leads to the detection of small tumour deposits, the significance of which remains uncertain. The aims of this study are to examine patients whose sentinel lymph nodes are positive for macro-metastasis, micro-metastasis or isolated tumour cells (ITCs) and to determine the rate of further nodal disease after axillary lymph node dissection (ALND).

Methods: A retrospective analysis of all patients undergoing a sentinel lymph node biopsy (SLNB) between January 2007 and December 2010 in a tertiary referral breast unit was performed. Patients who underwent an axillary lymph node dissection for macro-metastasis, micro-metastasis or ITCs were identified. Demographics, histological data and the rate of further axillary disease were examined.

Results: In total, 664 breast cancer patients attended the symptomatic breast unit during the study period, 360 of whom underwent a SLNB. Seventy patients had a SLNB positive for macro-metastasis. All of these patients underwent ALND. A positive SLNB with either micro-metastasis or ITCs was identified in 58 patients. Only 41 of the 58 patients went on to have an ALND, due primarily to variations in surgeons’ preferences. Nineteen patients with micro-metastasis underwent an ALND. Four patients had further axillary disease (21%). Twenty-two patients had ITCs identified, of whom only one had further disease (4.5%). No statistically significant difference was found between the two groups in terms of tumour size, grade, lymphovascular invasion or oestrogen receptor status.

Conclusion: ALND should be considered in patients with micro-metastasis at SLNB. It should rarely be employed in the setting of SLNB positive for ITCs.

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Introduction

Recent decades have seen a paradigm shift in the management of breast cancer. A more conservative surgical approach has been adopted for the management of not only the breast but also the axilla. The sentinel lymph node biopsy (SLNB) has become the standard of care for staging the axilla in clinically node negative patients. A positive sentinel lymph node biopsy

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has been associated with further axillary disease, earlier disease recurrence and a poorer overall survival rate.\textsuperscript{1-6} Traditionally, patients with positive SLNB have therefore been managed with completion ALND.

However, as a result of more extensive histological sampling and the immunohistochemical analysis of fewer nodes, smaller volumes of nodal metastatic disease are now being detected. Nodal metastases can be classified into three main groups: macro-metastases (deposits >2 mm), micro-metastases (0.2–2 mm) and isolated tumour cells (<0.2 mm). What these actually represent in terms of further nodal burden as well as disease-free and overall recurrence remains unclear.

For patients with macro-metastatic disease the standard of care remains an ALND. Similarly, patients with micro-metastatic disease have been shown to have a worse disease-free and overall survival. Therefore the recent American Society of Clinical Oncology (ASCO) guidelines recommend an ALND.\textsuperscript{7} However the significance of isolated tumour cells (ITCs) remains uncertain with some investigators suggesting they may predict the presence of additional nodal disease and earlier recurrence, while others regard patients with ITCs as being essentially “node negative patients” who do not require an axillary clearance.\textsuperscript{3,4,6,9}

The aims of this study are (i) to quantify rates of sentinel node positivity with respect to macro-metastases, micro-metastases and ITCs in our breast cancer patient population and (ii) to determine the appropriateness of further axillary surgery in the latter two groups.

Methods

A retrospective study of all breast cancers presenting to a symptomatic breast unit between January 2007 and December 2010 was performed. Patients with ITC or micro-metastasis on SLNB were identified from a prospectively maintained database. Patient demographic data, histological data and treatment modalities for the groups were collected and compared.

All patients who subsequently underwent an ALND for micro-metastatic disease or ITCs were included in the analysis. Demographic, histological and treatment modalities were documented. The rate of macroscopically positive non-sentinel lymph nodes within the ALND specimen were identified and compared between the two groups. All data were analysed using SPSS version 19.0.

Results

Data was collected from 664 breast cancer patients attending a symptomatic breast unit during the study period. A total of 360 sentinel lymph node biopsies were performed during this period. Seventy patients had a SLNB positive for macro-metastasis. Fifty-eight additional patients were identified with a positive SLN, 26 of whom had micro-metastatic disease (Group 1) with a mean age of 52 yrs, and 32 of whom had isolated tumour cells (Group 2) with a mean age 55 years. Demographics and tumour characteristics of the two groups were otherwise similar.

An ALND was performed in all patients with macro-metastatic disease, 25 of whom were found to have additional macro-metastases (36%). ALND was also carried out in 19 of 26 patients (76%) with micro-metastatic disease and 22 of 32 (69%) patients with isolated tumour cells. Patients with SLNB positive for micro-metastasis who did not proceed to ALND were all aged greater than 70 years or elected not to undergo the procedure. The decision to perform an ALND in the ITC group was based on the consultant surgeon’s personal preference for management of ITCs. In total, five surgeons operated on our cohort, two of whom advocated ALND for ITCs due to the unknown significance of these deposits. The remaining three surgeons did not perform ALND due to a lack of evidence supporting the procedure in patients with ITCs. Of the nineteen patients with micro-metastatic disease who underwent an ALND four had further macroscopically positive nodes on an ALND. One patient originally had a single sentinel node positive for micro-metastatic disease. In the subsequent ALND twenty-one lymph nodes were identified, of which one node was positive for macro-metastatic disease and one for micro-metastatic disease. The second patient had a solitary sentinel lymph node containing micro-metastases with a further two nodes positive for micro-metastases and one node for macro-metastases on ALND. The third patient had one of two sentinel lymph nodes positive for micro-metastases with a subsequent solitary lymph node containing macro-metastatic disease identified after ALND. The fourth patient had micro-metastases identified in a single sentinel lymph node. Subsequent ALND retrieved a further twenty-eight lymph nodes of which seven were found to contain macro-metastases.

Twenty-two patients with isolated tumour cells underwent an ALND (69%). One patient was found to have macro-metastases in two of the twenty-two axillary lymph nodes on subsequent ALND. Two other patients had further isolated tumour cell deposits within their ALND specimens.

A comparison of patients with micro-metastatic disease in the sentinel lymph node biopsy (Group 1) with those who had isolated tumour cells identified in the sentinel lymph node biopsy (Group 2) was performed. Patients in Group 2 were more likely to have undergone a mastectomy than those in Group 1 (\(p = 0.0228\)). There was no significant difference between the two groups with respect to the presence of DCIS (\(p = 0.5029\)), nor in the final histological diagnosis (invasive ductal carcinoma: \(p = 0.30\); invasive lobular carcinoma: \(p = 0.36\)). No significant difference was noted between the two groups in terms of tumour size (\(p = 0.9058\)) or tumour grade (\(p = 0.4436\)). There was a trend towards presence of lymphovascular invasion in Group 1 but this was not statistically significant (\(p = 0.062\)). There was no difference in rates of oestrogen receptor positivity between our two groups (\(p = 0.7239\)). Finally, patients in Group 1 were more likely to have macro-metastases in ALND nodes, however this was not statistically significant (\(p = 0.069\)).

A comparison of all patients who underwent an ALND for ITC and micro-metastasis with those who did not undergo an ALND was performed. No association was found between tumour grade (\(p = 0.3621\)), tumour size (\(p = 0.8076\)) or...
lymphovascular invasion (p = 0.5199) and an increased likelihood of having an ALND. There was no association between histological subtypes of breast cancer and the chance of undergoing an ALND.

Discussion

The management of breast cancer has changed dramatically in recent decades from a radical to a more conservative approach. The role of an ALND in patients with micro-metastatic disease or isolated tumour cells found on a sentinel lymph node biopsy is controversial. It remains difficult to determine whether performing a lymph node clearance on patients with minimal axillary disease substantially improves either their disease-free or overall survival. However, numerous recent studies have attempted to clarify this difficult issue.

Cyr et al. attempted to address this issue by comparing patients with isolated tumour cells and micro-metastatic disease on a sentinel lymph node biopsy who subsequently did and did not undergo an ALND. In total there were 116 patients with a sentinel lymph node positive for either micro-metastasis or ITCs, 55 of whom subsequently underwent an axillary lymph node dissection.1 Although a 24% rate of positive non-sentinel node involvement was found in the patients with isolated tumour cells on SLNB who underwent an ALND, there was no loco-regional or distant recurrence evident in the ITC group who had SLNB alone. In the micro-metastasis group, 37 patients did not have an ALND. Only one patient had an axillary recurrence following SLNB. One patient had a recurrence within the breast but no further axillary disease was found. A further patient died of distant metastases but had no evidence of axillary recurrence prior to this. The study concluded that omitting an ALND in patients with micro-metastases or ITC was not associated with a significantly higher likelihood of developing axillary recurrence.1

Conversely, the Oxford overview demonstrated that for every four local recurrences that are prevented over fifteen years, with either the use of surgery or radiotherapy, one death from breast cancer could be prevented. It is therefore important that we bear these results in mind before electing not to perform an ALND in patients with nodal metastases.20 The prevention of local recurrence, its association with mortality and the avoidance of long-term morbidity highlights the dilemma in undertaking an axillary clearance. What remains unclear is whether sentinel node positive patients (macro-metastasis) have an increased number of recurrences when axillary dissection is omitted.

The American College of Surgeons Oncology Group (Z0011 Trial) attempts to address this issue. Eight-hundred and ninety-one patients were randomised to either an ALND or only a sentinel lymph node biopsy for patients with either macro, micro-metastatic or isolated tumour cells within their sentinel nodes. They found additional nodal metastases in 27% of patients who underwent ALND. The authors found a low rate of loco-regional recurrence in all patients involved in the study, with similar rates of regional recurrence in both arms of the study suggesting that not all non-sentinel node metastases develop into clinically detectable disease. Therefore, they did not find any significant improvement in loco-regional control in patients treated with a complete lymph node dissection.11 The results of this trial need to be interpreted with caution. Patients included in this study were of early stage disease (T1, T2) who underwent breast conserving surgery only. In addition exclusion criteria included patients with bilateral or multi-centric breast cancer, those with a history of ipsilateral axillary surgery, or where the sentinel node was deemed positive on immunohistochemistry, all of whom were included in our study. Given the fact that this trial included a very selective group of patients, the results may not be applicable to our group of non-screen detected breast cancer patients.

Despite the increasing use of sentinel lymph node surgery only, significant numbers of patients are still returning to theatre to undergo a completion axillary dissection. Intra-operative assessment of the sentinel node may allow us to avoid this by performing a single stage surgery. The One Step Nucleic Acid Analysis (OSNA) study group recently published results of their multicentre prospective trial.22 A total of 204 breast cancer patients undergoing SLNB were recruited from four centres within the UK. Half of each SLN was assessed for cytokeratin 19 mRNA by OSNA. The remaining half of the SLN was paraffin embedded for intensive histological examination. Concordance rates of 96% were found for OSNA versus histopathological evaluation of the SLN (sensitivity 91.7% and specificity 96.9%). This technique may therefore allow accurate intra-operative diagnosis of nodal metastases and therefore immediate ALND in patients with a positive SLNB. However, there are limitations to the use of OSNA in this setting as a small number of breast tumours will not express cytokeratin 19 at all and its suitability for patients undergoing a SLNB post neo-adjuvant chemotherapy is questionable. Finally, the exact copy number of cytokeratin 19 which represents macro-metastatic, micro-metastatic disease or isolated tumour cells remains to be fully elucidated and therefore may be a rate-limiting step in its widespread introduction.

In this study, 25 patients had SLNB positive for micro-metastasis. Four out of 19 patients (21%) who underwent an ALND following a SLNB positive for micro-metastases were found to have further positive non-sentinel lymph nodes. In contrast, of the 32 patients with ITCs on SLNB, 1 out of 22 (4.5%) patients who underwent ALND were subsequently found to have further nodal disease. Although these results did not reach statistical significance, it points to a low rate of further axillary disease, particularly in patients with ITCs. The study was not designed to evaluate loco-regional control as the follow-up period is currently too short.

Conclusion

This study provides evidence that ALND remains a reasonable option in patients with micro-metastasis at SLNB. In those patients with ITCs at SLNB, ALND provides questionable benefit for the patient. We suggest that ALND be considered in patients with micro-metastasis at SNB, but should not be routinely employed in the management of patients with ITCs at SNB.
REFERENCES


