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Neill Patani, Kefah Mokbel

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# The clinical significance of sentinel lymph node micrometastasis in breast cancer

Neill Patani · Kefah Mokbel

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**Abstract** *Introduction* The advent of sentinel lymph node biopsy (SLNB) and improvements in histopathological and molecular analysis have increased the rate at which micrometastases (MM) are identified. However, their significance has been the subject of much debate. In this article we review the literature concerning axillary lymph node (ALN) MM, with particular reference to SLNB. The controversies regarding histopathological assessment, clinical relevance and management implications are discussed. *Methods* Literature review facilitated by Medline and PubMed databases. *Results* Published studies have reported divergent results regarding the significance and implications of ALN MM in general and sentinel lymph node (SLN) MM in particular. Some studies demonstrate no associations, whilst others have found these to be indicators of poor prognosis, associated with non-SLN involvement, in addition to local and distant failure. Absolute consensus regarding the optimal analytical technique for SLNs has yet to be reached, particularly concerning immunohistochemical (IHC) techniques targeting cytokeratins and the utility of contemporary molecular analysis. *Conclusion* SLN MM are likely to represent an incremental detriment to prognosis and increased risk of non-SLN involvement, despite only modest up-staging within current classification systems. In

the absence of level-1 guidance concerning the management of women with SLN MM, each case requires discussion with regard to other tumour and patient related factors in the context of the multidisciplinary team. Randomized studies are required to evaluate the prognostic significance and optimal management of each category of tumour burden within the SLN. The identification of MM remains highly dependent on the analytical technique employed and there exists potential for stage migration and impact on management decisions.

**Keywords** Breast cancer · Sentinel lymph node · Micrometastasis · Sentinel lymph node biopsy · Axillary lymph node dissection · Prognosis · Recurrence · Morbidity · Mortality · Evidence

## Introduction and background

ALN status at the time of diagnosis remains one of the most important prognostic indicators for women with breast cancer (BC) [1]. In addition, lymph node status can influence management decisions regarding adjuvant local and/or systemic therapies. Axillary lymph node dissection (ALND) remains the gold standard for axillary staging, however the morbidity of this procedure can be high. Large randomized controlled trials have confirmed the efficacy and reduced morbidity associated with sentinel lymph node biopsy (SLNB) as an axillary staging procedure [2]. SLNB now represents the standard of care for women with early stage BC which is clinically node negative. SLNB is not routinely necessary for patients with ductal carcinoma in-situ (DCIS), although it has been offered to individuals undergoing mastectomy or those with large, palpable, high-grade or recurrent lesions, in view of the risk of

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N. Patani · K. Mokbel (✉)  
The London Breast Institute, The Princess Grace Hospital,  
45 Nottingham Place, London W1U 5NY, UK  
e-mail: kefahmokbel@hotmail.com

N. Patani  
e-mail: neillpatani@hotmail.com

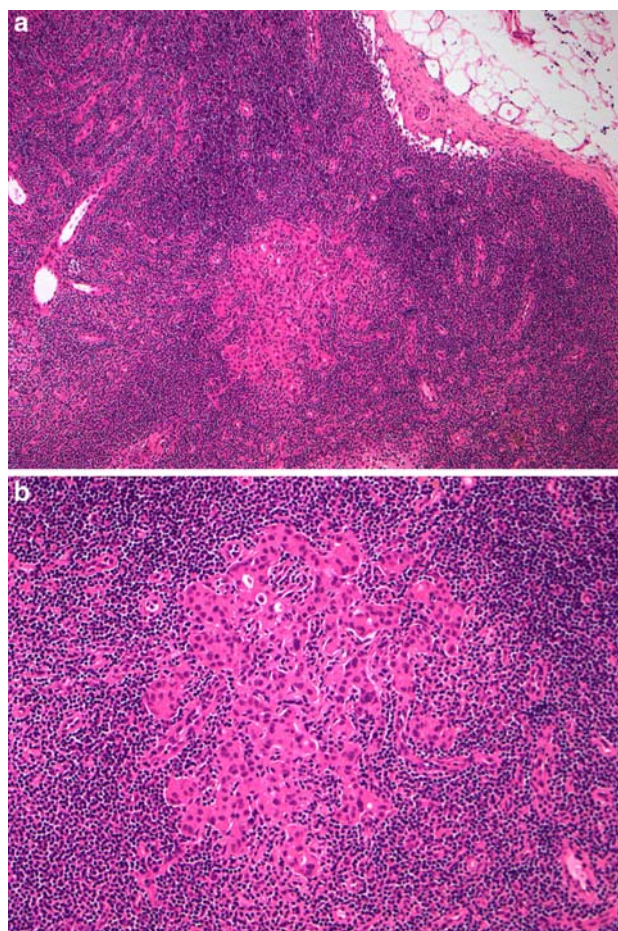
K. Mokbel  
St. George's University of London, London, UK

accompanying invasive disease [3]. In patients where the sentinel lymph node (SLN) is free of tumour, ALND is considered unnecessary. In cases where there is evidence of SLN involvement with tumour, axillary treatment is indicated, either in the form of ALND or radiotherapy (RT). The aim of such treatment is to reduce the risk of local recurrence (LR) within the axilla.

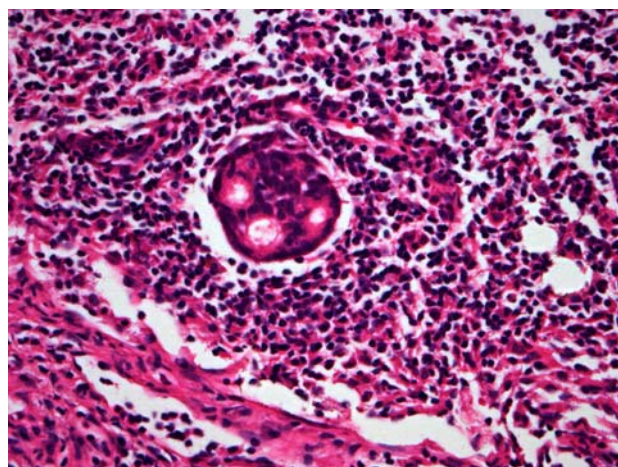
In addition to the patient centered advantages of SLNB, the procedure has significantly reduced the number of lymph nodes sent to the pathologist for staging purposes, from an average of 15–20 from ALND to 1–3 nodes from SLNB. The analysis of this material has also been facilitated by accompanying advances in molecular biology. In combination, these facts have allowed the pathologist to examine each lymph node in greater detail using a variety of techniques. Despite incremental improvements in sensitivity and specificity, the outcome of histopathological analysis is not always binary. This can have potentially significant implications, both for the surgical and adjuvant treatment of patients. The majority of SLNs can be classified as positive or negative, based on the presence or absence of macrometastasis. The management of these patients is supported by a large evidence base. However, a significant minority of SLNs are found to contain a micrometastasis (MM) or isolated tumour cells (ITC) (Figs. 1 and 2). These terms are defined by the American Joint Committee on Cancer (AJCC) as follows: macrometastasis ‘greater than 2.0 mm’, MM ‘greater than 0.2 mm but not larger than 2.0 mm’ and ITC ‘no larger than 0.2 mm’ [4, 5]. Small volume disease has also been incorporated into the TNM (UICC) classification and staging system, with pN1a or pNmi reflecting the presence of MM and pN0(i+) representing ITC [5]. However, the significance of SLNs which contain MM and/or ITC in the absence of macrometastasis has been the subject of much debate. In this article we review the literature concerning ALN MM, with particular reference to SLNB. The controversies regarding histopathological assessment, clinical relevance and management implications are discussed.

### Search strategy and selection criteria

Articles were identified by searches of MEDLINE and PubMed up to October 2007 using the terms: “breast cancer” or “sentinel lymph node” or “axillary lymph node” or “lymph node” and “micrometastasis” or “micrometastases” or “micro metastasis” or “micro metastases” or “micro-metastasis” or “micro-metastases” and “evidence” or “prognosis” or “morbidity” or “mortality” or “recurrence”. Studies identified were screened for those that focused on SLN micrometastasis. All randomized controlled trials and large retrospective series



**Fig. 1** Micrometastasis within a sentinel lymph node, haematoxylin and eosin stained: (a) low power and (b) high power



**Fig. 2** Isolated tumour cell within a sentinel lymph node, haematoxylin and eosin stained

were included. The reference articles in this review were selected to provide a balanced and representative overview of a complex subject with an extensive base of published work.

## Analysis of the sentinel lymph node

Various methods of histopathological analysis have been described in the literature and technological advances continue to drive the evolution of this process. Analysis of the SLN is often completed in two stages, firstly, intra-operative assessment is performed in order to provide immediate guidance to the surgeon with regard to the need for ALND. This is followed by the delayed definitive examination of permanent sections.

### Intra-operative analysis of the SLN

Intra-operative assessment often involves frozen section analysis [6], based on haematoxylin and eosin staining (HES) or the cytological assessment of touch-imprints [7]. Intra-operative frozen section analysis is cost effective and affords many advantages to both the patient and the surgeon. However, the technique is more demanding, requiring a skilled pathologist, and less accurate than formal examination of fixed material. In view of the false-negative rate associated with intra-operative techniques and subjective variations relating to their interpretation, attempts have been made to create more sensitive, accurate and objective methods of rapid detection. The intention is to avoid situations where the final histology differs from the intra-operative assessment, necessitating a further procedure for the patient. Recently, advances in molecular biology have enabled highly sensitive techniques to be applied to SLN analysis. Schoenfeld et al. [8] have used the reverse transcriptase polymerase chain reaction (RT-PCR) for cytokeratin 19 mRNA and found positive results in 15% of SLNs previously deemed to be negative. Kurosumi et al. [9] have recently reported the utility of a real-time RT-PCR method for the detection of SLN MM with a sensitivity and specificity of 89.5% and 96.7%, respectively, employing a frozen section based protocol. Using a one-step nucleic acid amplification (OSNA) based approach, Tsujimoto et al. [10] have established thresholds for cytokeratin 19 mRNA which can distinguish between macrometastasis and MM. Concordance with histopathological assessment was reported to be approximately 96% with no false positives. Ishikawa et al. [11] have recently employed a transcription-reverse transcription concerted reaction (TRC), targeted at carcinoembryonic antigen (CEA) mRNA, in order to reduce the false-negative rate associated with the routine analysis of SLNs. However, concerns exist regarding the utility of these approaches. Particular disadvantages include the fact that many of them do not permit morphologic correlation and often require destructive processing of the sample. False positive results can be caused by benign epithelial inclusions, benign mechanical transport of breast epithelium or extrinsic

contamination and so there is potential for erroneous upstaging [12, 13]. On the other hand, these amplification based techniques offer the potential to detect metastatic disease which can not be identified by conventional staining or immunohistochemistry (IHC).

### Definitive analysis of the SLN

Advances have also been made in the definitive assessment of fixed SLNs. Efforts have been made to reduce significant differences in the pathological processing of lymph node blocks. Various methods of histopathological examination with HES have been described including single level analysis, step sectioning and serial sectioning [14]. More recently the development of IHC techniques targeting epithelial cytokeratins has revolutionized the definitive assessment of SLNs, particularly those which appear negative with conventional HES based analysis. These approaches have enabled the detection of otherwise occult metastases and additional extremely small lesions which would otherwise have been missed. The Philadelphia consensus meeting [15] recommended that serial sections, less than 2 mm, were required for the reliable detection of macrometastasis. Significantly, the addition of IHC for cytokeratins (CK 19, CK AE1/3) was not routinely recommended. This is consistent with guidance from the American Society of Clinical Oncology [16]. The European recommendations [17] suggest screening for MM (>0.2 mm) and advise against routine IHC analysis. Using a geometrical model of spherical metastases randomly distributed within a lymph node, Cserni [18] has suggested that sections taken 1 mm apart would provide a reasonable means of detecting almost all macrometastases. In addition, a step sectioning protocol with levels of 200 microns would be sufficient to screen for MM. Such narrow sections are technically more difficult and labour intensive to prepare. However, in support of this, serial sectioning of the entire SLN with cytokeratin staining at narrow intervals has been reported to identify occult metastases in an extra 25% of patents [19]. This is consistent with other estimates in the literature which relate to the relative upstaging of previously negative lymph nodes [20, 21]. The addition of the aforementioned PCR based methods can significantly increase the apparent 'false-negative' rate of conventional analysis [22]. Multi-parameter flow cytometry, applied to permanently fixed sections, has also been shown to detect MM within SLNs [23]. Adjuncts to the conventional human assessment of specimens have been shown to be effective. Mesker et al. [24] demonstrated that supervised automated microscopy can increase the sensitivity and efficiency of detection of SLN MM and Weaver et al. [25] have described the utility of automated computer-assisted image analysis.

## The clinical significance of micrometastasis

Published studies have reported divergent results regarding the significance and implications of MM in BC. In the following, we consider the evidence for and against the clinical significance of ALN MM in general and SLN MM in particular.

### Evidence in favour

Intuitively one expects that the presence of metastases, regardless of size, will have a detrimental effect on patient outcome. Furthermore, the indication for many adjuvant local and/or systemic therapies is now based on the estimated risk of local and/or distant failure. Proponents argue that minimal volume disease should be actively sought and factored into making management decisions. Some of the earliest studies comparing node negative women to those with ALN MM found associations with poorer prognosis [26]. Fisher et al. [27, 28] also reported higher rates of recurrence and death from BC in those with MM compared to those with negative nodes after an average follow-up of 4 years. More recently, Chen et al. [29] have utilized the surveillance, epidemiology and end results (SEER) database, including over 200,000 patients, to demonstrate that nodal MM carries a prognosis intermediate to N0 and N1 disease, even after adjusting for patient and tumour related variables. The tumour burden of ALNs appears to be inversely correlated with prognosis, even when the tumour burden is very small [29]. A large retrospective study involving over 10,000 patients with BC over 25 years found that patients with a solitary MM had a poorer prognosis than those without, although this only reached statistical significance in the group who did not have systemic adjuvant treatment. Furthermore, in patients who did not receive adjuvant systemic therapy, the prognosis of a single MM was comparable to a single macrometastasis [30]. Negative prognostic impact has also been reported by Reed et al. [31]. In their study of 385 women with BC, poorer prognosis was found in those 45 cases with occult metastases compared to their truly node negative counterparts. Cote et al. [20] found that patients which were retrospectively found to have ALN MM, had a worse overall survival than others enrolled in the same adjuvant therapy trial who were node negative. A case controlled study of 96 patients with 15 year follow-up has found that occult MM in ALNs appears to predict subsequent distant metastases in patients with stage 1 BC [32]. There are several other studies which have found a significantly poorer prognosis associated with MM [33, 34]. In a prospective study of women with stage 1 BC, the International Ludwig Breast Cancer Study Group reported a 5-year disease free survival of 58% in patients with MM

compared with 74% in those without and overall survival rates of 79% and 88%, respectively [35]. In a study of 1,959 consecutive patients, Calceoni et al. [36] reported a significantly reduced disease-free survival and increased risk of distant metastases in patients with MM after a median follow-up of approximately 50 months. Umekita et al. [37] have demonstrated that disease free survival and overall survival, after a median follow-up of 98.5 months, were significantly better in patients without MM, 71% vs. 93% and 76% vs. 96%, respectively. Other reviews have also concluded that patients with MM detected by serial sections and IHC performed on HES negative nodes remained at a definite survival disadvantage [38]. A meta-analysis of all studies from 1966 to 2003 has concluded that the majority of studies have found MM to be associated with a significantly poorer prognosis and in some cases this difference could only be identified after prolonged follow-up. The presence of MM should therefore be taken into consideration when making decisions about patient management [39].

The advent of SLNB, alongside advances in analytical techniques, now enable the histopathologist to perform a more detailed evaluation of considerably fewer lymph nodes which are most likely to contain metastasis. Consequently, the diagnosis of SLN MM has significantly increased in frequency [29]. However, the clinical significance and implication of such small volume disease has been the subject of much debate. Studies which have found SLN MM (as defined by the AJCC) to have particular prognostic utility are listed in Table 1. Mullenix et al. [40] performed cytokeratin IHC on SLNs which appeared negative on HES staining and found that this small proportion of patients (4.4%) had a significantly increased risk of distant metastases. The risk of non-SLN involvement has been found to be significantly higher in women with SLN MM [41]. SLN MM and increasing MM size have been identified as significant predictors of non-SLN metastasis [42]. This relationship can be considered as a continuous variable where SLN MM are significantly associated with non-SLN involvement [43]. In fact, Viale et al. [44] reported the overall rate of non-SLN positivity to be 16% in those patients with SLN MM less than 1 mm compared to 32% for those with SLN MM > 1 mm. Dabbs et al. [45] found 10 of 112 patients (9%) with SLN MM to have non-SLN macrometastasis. In keeping with this, Leidenius et al. [46] found 25% of patients with SLN MM to have residual disease in the axilla. Schrenk et al. [47] have compared patients with SLN MM to those with SLN macrometastases undergoing ALND. Non-SLNs were found to be positive in 18% of those with SLN MM compared to 51.1% of those with macrometastasis. The size of MM and the presence of lymphovascular invasion were significantly related of the risk of finding non-SLN

**Table 1** Studies providing evidence supporting the significance of SLN MM

Author [Ref.]	Year	Total patient no.	Cases with SLN MM	Outcome measure
Mullenix [40]	2005	334	4	Local recurrence/distant failure
van Rijk [41]	2006	2,150	148	Non-SLN involvement
Houvenaeghel [50]	2006	700	700	Non-SLN involvement
Di Tommaso	2006	540	62	Non-SLN involvement
Schrenk [51]	2005	379	138	Non-SLN involvement
Leidenius [46]	2005	84	84	Non-SLN involvement
Viale [42]	2005	1,228	318	Non-SLN involvement
Giard [48]	2004	542	55	Non-SLN involvement
Dabbs [45]	2004	445	49	Non-SLN involvement
den Bakker [49]	2002	32	32	Non-SLN involvement
Viale [44]	2001	634	109	Non-SLN involvement
Turner [43]	2000	194	93	Non-SLN involvement

involvement in women with SLN MM. Even in patients with small MM (<0.5 mm) and no evidence of lymphovascular invasion, the risk of non-SLN involvement was 8.5%. In their study of 542 women with BC, Giard et al. [48] identified 55 cases of SLN MM of which 40 underwent ALND and 6 were found to harbour additional metastatic foci. Similarly, den Bakker et al. [49] identified one or more involved non-SLN in approximately one-third of their 32 patients with SLN MM. Furthermore, within those with SLN MM no subgroup of tumour size or grade could be identified that did not have non-SLN involvement. Interestingly, Houvenaeghel et al. [50] found that the method employed for MM detection was a significant predictive factor for non-SLN involvement. Furthermore, Tommaso et al. [51] demonstrated that the anatomical location of MM within the SLN was an independent predictor of non-SLN involvement, with intranodal lesions being more strongly associated with non-SLN metastasis than sinusal lesions.

#### Evidence against

Some authors have called into question the clinical relevance of such small metastatic foci [52, 53], advising caution in their use when making decisions about offering or withholding established therapies. Many of these local and/or systemic therapies are based on a large body of level-1 evidence generated prior to the MM era. Considering the evidence against ALN MM in general, Tjan-Heijnen et al. [54] in their review of eight studies, each with at least 100 patients and 5 years follow-up, concluded that there was insufficient evidence to confirm that MM were of prognostic utility. However, it is noteworthy that none of the studies reviewed employed the presently accepted definition of MM. Indeed, there are many examples in the literature where the definition of MM has differed; some authors have based the definition on the percentage of the

cross-sectional area of the SLN involved, in addition to various references to occult metastasis [12]. De Mascarel et al. [55] compared 120 women with MM to those with NO disease, median follow-up 7 years, and found that statistically significant associations with survival which were identified on univariate analysis did not remain after multivariate analysis. A lack of significant associations has also been reported by several other studies [56–58].

Several authors have also found MM to have limited utility with particular reference to SLNB. Studies which have not found SLN MM (as defined by the AJCC) to have clinical utility are listed in Table 2. A prospective study of 150 patients undergoing SLNB alone found no difference in the development of axillary recurrence between those with MM and those without after a median follow-up of 42 months [59]. In a study of 39 patients with SLN MM who did not undergo ALND, median follow-up of 32 months, Guenther et al. [60] have found no axillary recurrence and only a single case of distant failure. Similarly, in a series of 27 patients followed up for 30 months, Fant et al. [61] found no cases of axillary recurrence in those with SLN MM. In a smaller study including 15 patients with MM, 11 of which underwent ALND, no cases of local or systemic relapse were identified after a median follow-up of 13.5 months [62]. In a retrospective review, Rutledge et al. [63] found that the risk of finding non-SLN positivity was significantly lower in patients with SLN MM (3%) compared to SLN macrometastasis (63%). The authors concluded that careful assessment of risk versus benefit should be undertaken in view of the known morbidity of ALND. Hence in some studies the incidence of non-SLN metastasis in patients with SLN MM appears to be comparable to the false negative rate of SLNB itself. These findings are consistent with those of Fournier et al. [64] who reported only 1 case of non-SLN metastasis in 16 women undergoing ALND for SLN MM and no cases of local recurrence in any of the patients with SLN MM, including

**Table 2** Studies providing evidence against the significance of SLN MM

Author [Ref.]	Year	Total patient no.	Cases with SLN MM	Outcome measure
Nagashima [82]	2006	375	19	Local recurrence/distant failure
Langer [59]	2005	234	27	Local recurrence/distant failure
Guenther [60]	2003	46	16	Local recurrence
Fant [61]	2003	31	27	Local recurrence
Rutledge [63]	2005	358	29	Non-SLN involvement
Fournier [64]	2004	194	21	Non-SLN involvement
Ganaraj [83]	2003	305	41	Non-SLN involvement
Liang [62]	2001	227	15	Non-SLN involvement
Chu [81]	1999	157	69	Non-SLN involvement

8 additional patients with SLN MM who did not undergo ALND. Interestingly, Wong et al. [65] have found that SLNs positive only on IHC were not of prognostic significance. However, it is noteworthy that many of the studies which have failed to assign significance to SLN MM are comparatively small in patient number and hence may not have been adequately powered to identify any difference. In some cases the length of follow-up may also have been inadequate for the detection of local or distant recurrence.

In DCIS, IHC can identify MM in up to 9% of patients [66] which is clearly in excess of the accepted rate of lymph node involvement. In another study of 102 patients with DCIS and negative axillary nodes, MM were identified in 13% on retrospective analysis. After 10–28 years of follow-up, the overall disease recurrence rate was 12% although none of these patients had been found to harbour MM and the recurrence site was not found to be the axilla in any case [67]. The low rate of local recurrence and excellent overall survival in these patients has been suggested to provide further circumstantial evidence against the significance of MM. However, DCIS is a clinically heterogeneous lesion, the natural history of which remains elusive [3]. Hence, it may not be appropriate to make inferences about MM, given the extent to which the tumour biology of DCIS is likely to differ from BC.

## Discussion

The last two decades have seen a paradigm shift in the management of women with breast cancer. Late presentation, delayed diagnosis and radical ablative surgery to the breast and axilla have been replaced by an effective national screening programme, prompt diagnosis, breast conservation and a more targeted approach to the axilla. One of the key drivers of this change has been an improved understanding of the natural history and tumour biology of BC. The ‘mechanistic’ model for progression hypothesized

the centrifugal spread of metastases from station to station in a cumulative manner and this provided the justification for type of surgery advocated by Halsted [68]. More recently, we have come to accept a more ‘biological’ model which considers BC as a systemic disease with disseminated MM at the time of diagnosis [27, 28]. It has been suggested that the behavior of these MM is a key determinant of overall patient prognosis. Hence, modern surgical intervention aims to provide local control and no longer aspires to eradicate all disease. It is noteworthy that additional foci of carcinoma have been identified in over 60% of mastectomy specimens, approximately 80% of which lie outside the index quadrant [69, 70]. Landmark trials such as the NSABP-B06 suggest that following breast conserving surgery, such remote foci may be adequately treated by adjuvant radiotherapy [71]. The implication is that these incidental lesions may be of low malignant potential and uncertain clinical relevance. By providing local control, surgical intervention reduces patient morbidity in the long term and supplies material for staging purposes. The analysis of surgical specimens serves to categorize patients into those with ‘good’ or ‘poor’ prognosis and their risk of local or distant failure provides the justification for adjuvant local or systemic treatments. These therapies can target systemic micrometastatic disease and thereby afford improvements in survival. Although the concept of SNLB is largely a product of the ‘mechanistic’ model, in modern surgical practice it is employed purely as a staging procedure to guide ALND or axillary RT. Advances in molecular biology and IHC, combined with the practicality of performing a more detailed analysis on a single SLN, have increased the likelihood of finding MM. In fact the frequency of this diagnosis has increased substantially and is likely to continue doing so with each advance in analytical techniques. It seems somewhat paradoxical that women are now presenting with earlier stage primary tumours and yet there is a trend to increase the apparent stage at diagnosis by

improvements in SLNB analysis. The impetus to determine the significance these lesions has also increased. MM found within the SLN could influence decisions regarding the further management of the axilla. However, in the era when ALND was the standard of care, MM found incidentally within the clearance specimen would be unlikely to have a significant impact on patient management.

Controversy exists surrounding the best management of patients with SLN MM, in terms of further axillary surgery or radiotherapy and/or systemic adjuvant treatment. The fundamental question arises as to why we should consider treating micrometastatic disease within the SLN differently to that found elsewhere. It may be rational to rely on systemic adjuvant treatments to perform in the axilla as they do elsewhere and SLN MM could simply represent an indication for systemic adjuvant therapy. The counter argument is that ALND or axillary radiotherapy should reduce loco-regional recurrence in patients with SLN MM, given their association with non-SLN involvement. Loco-regional recurrence can be particularly problematic to manage and is associated with poor prognosis. In fact, all reviewed studies including more than 70 patients with SLN MM support the argument that such small volume disease should be actively sought and incorporated into our axillary management strategy (Table 1 and 2). The added value of further axillary surgery in the form of ALND in women with SLN MM, now needs to be formally quantified by appropriately powered studies. The relative reduction in the number of ALNDs performed over the last decade is supported by a large evidence base and improvements in the detection of SLN MM have the potential to drive management back towards an increased use of ALND. Since SLN MM are most commonly confirmed following complete pathological assessment, any further axillary surgery would need to take place on a second occasion.

An alternative could be to offer patients with SLN MM axillary radiotherapy. There is some evidence to support the management of women who are clinically node negative with axillary radiotherapy only. A study with 15 years of follow-up has found no difference in survival between clinically node negative women with early breast cancer managed with ALND or axillary radiotherapy, although a slightly higher rate of axillary recurrence was noted [72]. However this may be an equitable solution, in view of the fact that MM are likely to represent a lower risk of local and distant failure than macrometastasis and women could be spared the morbidity of ALND. However, at present, further intervention for women with SLN MM is primarily surgical in the form of ALND, rather than axillary radiotherapy. Randomised controlled trials are required to clarify the optimal management of patients with SLNs which contain MM in the absence of macrometastasis. In addition to their association with non-SLN involvement,

SLN MM have been found to be indicators of poor prognosis, associated with local and distant failure. Tumour burden within the SLN is likely to represent a continuous variable extending from the presence of ITC to MM and macrometastasis. The relative importance of SLN tumour burden now needs to be determined in the context of other established patient and tumour related prognostic variables in order to provide an overall 'risk estimate'. This could be used to inform decisions regarding the risk/benefit of potential local and/or system interventions. Such information will need to be carefully considered in the context of the multidisciplinary team in order to make decisions regarding patient management.

In addition to the importance of SLN identification and retrieval during surgery, the reliable histological assessment and accurate determination of SLN involvement is obviously of critical significance. It is therefore somewhat surprising that whilst surgical technique has been relatively well standardized, absolute consensus regarding the optimal analytical technique has yet to be reached. The most effective technique for assessing the SLN will depend on the nature of the lesion that needs to be identified, hence decisions need to be made about the necessity of identifying MM and ITC [12]. Cserni et al. [73] has demonstrated discrepancies in the current practice of SLN evaluation, in addition to inconsistency regarding the categorization of MM amongst pathologists presented with identical digital images. As HES is increasingly complemented by IHC and molecular amplification techniques, including PCR and RT-PCR, subgroups of patients will be identified in which MM are only detectable by one modality or the other. 'Positivity' can therefore be categorized according to the modality employed. Some authors have assigned greater significance to MM which are visible on HES rather than those which require IHC for detection [74]. However the significance of MM detectable by particular modalities has not been determined and hence this information is not currently included in the TNM classification [75]. Current prospective studies include ACOSOG Z0010, in which patients with MM found only by SLN IHC will not undergo further axillary surgery, but may have breast radiotherapy or systemic adjuvant treatment. Results from the NSABP B-32 trial will also be relevant as patients were randomized to SLNB (proceeding to ALND for cases which were positive on HES) or routine ALND. Postoperative IHC analysis will identify some additional patients with MM whose long term follow-up with regard to local and distant relapse will be of particular interest. For the time being the further management of the axilla is likely to remain dependent on the extent of SLN 'positivity' or tumour burden rather than the technique employed for detection.

It is also noteworthy that several reports have identified associations between percutaneous biopsy of the primary

tumour and SLN involvement with tumour, including MM [76, 77]. Moore et al. [78] found that the presence of MM was significantly related to the method of breast biopsy, however this relationship was only observed for IHC detected MM rather than those identified by HE staining. However, in a study of 89 patients, Kinoshita et al. [79] have recently reported no association between preoperative FNA and the frequency of MM or survival of patients with early breast cancer. The spread of epithelial cells to axillary lymph nodes may also be attributable to benign mechanical transport [80].

### Conclusions and recommendations for practice

The prognosis for women with MM within the SLN should not be considered to be the same as those without. SLN MM are likely to represent an incremental detriment to prognosis and increased risk of non-SLN involvement, despite only modest up-staging within current classification systems. Management need not be altered for women in whom further axillary treatment with ALND or radiotherapy and systemic adjuvant treatment are already indicated. However, in the absence of level-1 guidance concerning the management of women with SLN MM, each case requires discussion with regard to other tumour and patient related factors in the context of the multidisciplinary team. Whilst there may exist a minimum tumour burden within the SLN for which further treatment can be safely omitted, this critical amount has yet to be defined. If the outcomes for current trials, including the NSABP B-32 and ACO-SOG Z0010, do not provide authoritative guidance, they may at least provide ethical and clinical justification for further randomized studies to evaluate the prognostic significance and optimal management of each category of tumour burden within the SLN.

The identification of MM remains highly dependent on the analytical technique employed and there exists potential for stage migration and impact on management decisions. Guidance relating to the histopathological analysis of SLNs has not been consistent, particularly concerning IHC techniques targeting cytokeratin, despite the fact that minimal metastatic disease is unlikely to be detected unless they are employed. Molecular technologies for the detection of MM which are ‘missed’ by conventional methods and/or IHC should only be used for research purposes at present.

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