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Running Head: Sentinel Lymph Node Isolated Tumour Cells

Article Type: Review

## Abstract

### Introduction

The advent of sentinel lymph node biopsy (SLNB) and improvements in histopathological and molecular analysis have increased the rate at which isolated tumour cells (ITC) are identified. However, their biological and clinical significance has been the subject of much debate. In this article we review the literature concerning SLNB with particular reference to ITC. The controversies regarding histopathological assessment, clinical relevance and management implications are explored.

### Methods

Literature review facilitated by Medline, PubMed, Embase and Cochrane databases.

### Results

Published studies have reported divergent results regarding the biological significance and clinical implications of ITC in general and SLN ITC 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 recurrence and distant disease. Absolute consensus regarding the optimal analytical technique for SLNs has yet to be reached, particularly concerning immunohistochemical (IHC) techniques targeting cytokeratins and contemporary molecular analysis.

**Conclusion**

The clinical relevance of ITC within the SLN should be primarily determined by the magnitude of their impact on patient management and outcome measures. The modest up-staging within current classification systems is justified and reflects the marginally poorer prognosis for women with SLN ITC. Management need not be altered where further axillary treatment with surgical clearance or radiotherapy and systemic adjuvant treatment are already indicated. However, in the absence of level-1 guidance, each case requires discussion with regard to other tumour and patient related factors in the context of the multidisciplinary team. The identification of ITC remains highly dependent on the analytical technique employed and there exists potential for stage migration and impact on management decisions. Evidence supporting the routine analysis of deeper tissue sections by IHC is lacking and molecular technologies should be restricted to research purposes at present.

**Key Words**

Breast cancer, isolated tumour cells, sentinel lymph node, sentinel lymph node biopsy, axillary lymph node dissection, prognosis, recurrence, morbidity, mortality, evidence.

## Introduction & Background

Axillary node status remains an important prognostic indicator in breast cancer (BC) [1]. Axillary lymph node dissection (ALND) remains the gold standard for staging, however, sentinel lymph node biopsy (SLNB) represents the standard of care for clinically and radiologically node negative disease [2]. Where the sentinel lymph node (SLN) is tumour free, ALND is considered unnecessary; otherwise intervention is indicated with ALND or radiotherapy (RT). The number of involved nodes informs decisions regarding adjuvant local and/or systemic therapies. Furthermore, ALND and RT provide loco-regional control, reducing disease burden and axillary local recurrence (LR).

Whilst the patient centered advantages of SLNB were anticipated, unforeseen consequences have resulted from the reduced number of nodes sent for pathological analysis. Submitted nodes are more likely to be biologically relevant with greater pathological yield than non-sentinel samples. Analysis has been facilitated by advances in molecular biology and rapid throughput technologies. Pathologists now examine nodes more extensively and in greater detail using multiple techniques. Unexpectedly, histopathological analysis has evolved away from conventional binary/dichotomous outcomes and become complicated by increasing identification of 'small-volume nodal metastases' [3]. The majority of SLNs remain positive or negative, based on 'large-volume' or macro-metastasis, with management supported by an extensive evidence base. However, an increasing minority harbor micro-metastasis (MM) or isolated tumour cells (ITC) (Figures 1-3), defined by the

American Joint Committee on Cancer (AJCC): macro-metastasis ‘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’ [4-7]. Similarly, the pathological tumour node metastasis (pTNM) (UICC) classification and staging system, with pN1a or pNmi reflecting MM and pN0(i+) for ITC [5-7]. The defining thresholds for boundaries between each category have arisen from expert consideration of the literature and build upon past precedent. The clinical significance of MM and/or ITC in the absence of macro-metastasis and the ‘stage migration’ away from nodal-negativity have been the subject of much debate [8-10]. Despite the lack of level-1 evidence guiding clinical practice, the somewhat arbitrary distinction between MM and ITC has become factored into management decisions. SLN MM are more likely to be considered relevant with consequent treatment (ALND or RT) and influence adjuvant therapy decisions [11]. On the contrary, SLN ITC are frequently disregarded and managed as node-negative [10-13]. In this article we review the literature concerning SLNB and ITC. The controversies regarding histopathological assessment, clinical relevance and management implications are explored.

## Search Strategy and Selection Criteria

Articles were identified by searches of Medline, PubMed, Embase and Cochrane databases up to February 2011 using the terms: “breast cancer” or “sentinel lymph node” or “axillary lymph node” or “lymph node” and “isolated tumour cells” and “evidence” or “prognosis” or “morbidity” or “mortality” or “recurrence”. Studies identified were screened for those that focused on sentinel lymph node isolated

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

## Analysis of the Sentinel Lymph Node

Intra-operative assessment often involves frozen section analysis [14], based on haematoxylin and eosin staining (HES) or the cytological assessment of touch-imprints [15]. Recent advances in molecular biology permit highly sensitive and rapid SLN analysis. Schoenfeld et al. [16] employed the reverse transcriptase polymerase chain reaction (RT-PCR) for cytokeratin (CK) 19, finding positivity in 15% of previously 'negative' SLNs. Similarly, Kurosumi et al. [17] report a sensitivity and specificity of 89.5% and 96.7%, employing real-time RT-PCR. Using one-step nucleic acid amplification (OSNA), Tsujimoto et al. [18] have established thresholds for SLN tumour burden, with 96% histopathological concordance and no false positives. Ishikawa et al. [19] have reported a transcription-reverse transcription concerted reaction (TRC) for carcino-embryonic antigen (CEA) mRNA, reducing false negatives. However, concerns exist regarding the utility of these approaches, including: destructive sample processing, lack of morphologic correlation, false positives from benign epithelial inclusions and unreliable determination of SLN tumour burden [20,21].

Various sectioning protocols facilitate the delayed definitive assessment of fixed SLNs, including step- or serial- processing, sampling fractions of the node volume.

However, absolute consensus regarding the optimal analytical technique has yet to be reached. The lack of uniform practice and reproducibility of the threshold distinguishing ITC from MM has been acknowledged by the European Working Group for Breast Screening Pathology (EWGBSP) [5-7,22-26]. Notably, standardised histologic criteria and image-based training can improve inter-observer reproducibility [27], providing an opportunity for updated staging manuals to address the issue of consistency. Immuno-histochemical (IHC) techniques targeting epithelial cytokeratins have revolutionized the definitive assessment of SLNs negative with HES [28-30]. The Philadelphia consensus meeting [12] recommended that serial sections <2 mm were required for reliable detection of macro-metastasis. Significantly, the addition of IHC for CKs (CK19, CKAE1/3) was not routinely recommended, consistent with guidance from the American Society of Clinical Oncology [13]. The European recommendations [8] also suggest screening for MM and advise against routine IHC analysis. Cserni [31] has recommended 1 mm sections for detecting almost all macro-metastases, with the addition of a 200 micron step-sectioning protocol to screen for MM. Serial-sectioning with CK-staining can identify occult metastases in an extra 25% of patents [32-35]. The addition of PCR or flow cytometry can significantly reduce conventional 'false-negative' rates [36,37]. Adjuncts to human assessment have also been shown to be effective; including supervised automated microscopy [38] and automated computer-assisted image analysis [39]. However, Cserni et al. [40,41] suggest that none of the current workable sampling strategies reliably disclose all ITCs. Hence, detecting ITCs remains a statistically random event and should not be considered the aim of SLN analysis [9,22]. The impetus must therefore be to determine clinically relevant levels of SLN

tumour burden, prior to embarking upon any consensus for reliable or standardised detection which could be time-intensive and cost prohibitive [9,20].

## Significance of Isolated Tumour Cells

### Evidence Against

The clinical relevance of small-volume nodal disease has been questioned [42,43]. Established local and/or systemic therapies are based on a large body of level-1 evidence generated prior to the ITC era. In their study of 174 patients, Ryden et al. [28] identified 6 with SLN ITC, none of which had further positivity on subsequent ALND. Chu et al. [44] reported non-SLN metastasis in only 6% of SLN ITC cases. Indeed, several studies find the incidence of non-SLN metastasis comparable to the accepted false negative rate of SLNB, arguing that ALND is not indicated in such cases. In another study of 165 patients with histologically negative SLNs, re-examination with IHC identified ITC in 17 and MM in 1 patient; however no significant difference in recurrence free survival (RFS) was identified, advocating management as node-negative patients [45].

Calhoun et al. [46] also concluded that ALND represented over-treatment. In 634 patients, 12.3% (78 women) had SLN ITC, 61 underwent ALND and only 3 (4.9%) had non-SLN involvement (1 macro-metastases and 2 MM). After a mean follow-up of 80.5 months no recurrence was identified, including those refusing ALND. Pugliese et al. [47] identified 86 patients with SLN ITC within their prospective

registry. After a median follow-up of 45.4 months, no statistically significant difference was noted in overall survival (OS) or RFS when comparing node-negative, SLN ITC and SLN MM patients. However, patients with small volume nodal disease were significantly more likely to receive adjuvant local and systemic treatments. Guenther et al. [48] followed 46 SLN positive women who did not undergo ALND, 23 had cellular metastases only detectable by IHC, 16 had MM and 7 had macro-metastases. After a mean follow-up of 32 months, no case of axillary LR had been identified. Hansen et al. [49] found the prevalence of SLN ITC to be 10.6% in their prospective cohort with a non-SLN involvement rate of 4%. After a median follow-up of 72.5 months patients with SLN ITC (n=84) or SLN MM (n=54) had the same OS and DFS as patients with negative SLNs. The majority of patients received adjuvant systemic therapy; 92% of those with ITC vs. 66% of those node-negative. Tjan-Heijen et al. [50] have reviewed 8 studies, each with >100 patients and 5 years follow-up, concludeding that there was insufficient evidence that MM and ITC were of prognostic significance.

Recently, prospective clinical outcome data have been reported from clinically node-negative patients within the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-32, randomising women to SNLB+ALND or SLNB alone. CK IHC performed at two additional tissue levels identified occult metastases in 15.9% of initially negative SLNs, of which 11.1% (n=430) were classified as harboring ITC clusters. Comparing ITCs with no metastases demonstrated increased hazard ratios (HR) for death (HR 1.27, CI 1.04-1.54), any outcome event (HR 1.18, CI 1.02-1.33) and distant disease (HR 1.19, CI 1.00-1.41). However, the reduction in OS was marginal (0.6% at 5-years) and insufficient to justify routine analysis of deeper tissue

sections or IHC for conventionally negative SLNs. Furthermore, subgroup analysis confirmed that ITCs had less impact than MM on every outcome evaluated, supporting the current segregation of categories and arguing against the need for any change in the management of women with SLN ITC [51].

**Evidence In Favour**

Intuitively the presence of metastases, regardless of size, implies access to lymphatic or blood vessels and this breach of a line of defence in the metastatic pathway is expected to worsen prognosis [52]. Many adjuvant local and/or systemic therapies are now indicated by the risk of local and/or distant failure. Proponents argue that minimal volume disease should be actively sought and factored into management. Van Deurzen et al. [53] in their systematic review of 29 articles, including 836 patients, found the prevalence of SLN ITC to be 6.7% and risk for non-SLN involvement to be 12.3% (95% CI, 9.5-15.7). This risk was lower than the non-SLN involvement rate for SLN-MM, but higher than accepted false-negative rates for SLNB. Furthermore, 64% of non-SLN involvement was macro-metastatic, implying that patients with SLN ITC without pre-existing indications for adjuvant systemic therapy might justify ALND. A meta-analysis has estimated the risk of non-SLN positivity to be 9-10% in those with SLN ITC [54]. Cserni et al. [40,41] found SLN ITC to be associated with a non-SLN metastatic rate of 8.5-13.5%. The French multi-centre study reported relatively high rates (16%) of non-SLN metastases associated with SLN ITC, without a statistically significant difference between ITC and MM for predicting non-SLN positivity (16% vs. 14.3%) [55]. Interestingly, the detection method was a significant predictor of non-SLN involvement. Lesions <0.2 mm

detected by HES carried a predictive value equivalent to MM, whereas IHC detection carried lower predictive value. This study has been criticized as accurate size was only available for 70% of cases [40,41]. However, their findings are consistent with the 14.7% non-SLN rate identified by the European Institute of Oncology, which found the prevalence of SLN ITC to be 9.4% (116 patients) [29,56]. SLN tumour burden emerged as a significant predictor of non-SLN involvement, which again was mostly macro-metastatic. No statistically significant difference found between SLN ITC and MM in terms of predicting non-SLN involvement (14.8% vs. 21.4%), however both were significantly less predictive than SLN macro-metastases [29]. The authors suggest that the rate of non-SLN involvement may be underestimated as non-SLNs are not routinely examined with the same scrutiny as SLNs.

Houvenaeghel et al. [57] have published a nomogram predicting non-SLN involvement. ITC emerged as a significant predictor, associated with a non-SLN rate of 14.3%. Schrenk et al. [58] reported a 9% rate of non-SLN involvement in 44 patients with SLN ITC. In both cases the majority of non-SLN deposits were macro-metastases. Leidenius et al. [59] prospectively followed a cohort of pT1 tumours over a median of 55 months. The prevalence of SLN ITC was 5.4%, 63 women were confirmed to have SLN ITC only (non-SLN negativity verified by ALND) compared to 868 with negative nodes. SLN ITC impacted upon management and adjuvant systemic treatment was given significantly more often (87% vs. 51%). Whilst no difference was noted in terms of OS or five-year RFS, those with SLN ITC had significantly worse five-year BC specific survival (95.2% vs. 98.4%) and were more likely to develop distant metastases within 5 years (8.1% vs. 1.9%). It is noteworthy that these differences were noted in spite of more frequent adjuvant systemic therapy.

De Boer et al. [60] recently reported on a large study (MIRROR) comparing the disease free survival (DFS) of 856 patients with node-negative disease (treated without adjuvant therapy), 856 patients with ITC or MM (treated without adjuvant therapy) and 995 patients with ITC or MM (treated with adjuvant therapy). After a median follow-up of 5.1 years the adjusted HR for disease events amongst those with ITC who did not receive systemic therapy compared to node-negatives was 1.50 (95% CI, 1.15-1.94), comparable to those with MM (HR 1.56, 95% CI, 1.15-2.13). Interestingly, those with ITC or MM who received adjuvant treatment faired significantly better than those receiving no adjuvant treatment (HR 0.57, 95% CI, 0.45-0.73). Again the HRs were comparable for ITC and MM, calling into question the relevance of current thresholds which define small-volume nodal disease. The authors conclude that ITC or MM were associated with a reduced five-year DFS in women with favourable early stage BC who did not receive adjuvant therapy. The level of tumour burden, ITC or MM, did not impact significantly on outcome, with comparable detriment to DFS. DFS was found to be improved by systemic adjuvant treatment [60].

Querzoli et al. [61] found ITC to be prognostic indicators of DFS and metastatic relapse. After a median follow-up of 8 years, the HR for all adverse events of pN0i+ compared to node negative patients was 2.51 ($p < 0.05$). No statistically significant difference was found between ITC and MM. Tan et al. [62] re-evaluated a historic cohort of axillary tissue from 368 node-negative patients treated by mastectomy, ALND and no adjuvant local or systemic therapy. The prevalence of axillary ITC was found to be 17% (61 patients). The 15-year DFS for the ITC group was worse than the node-negatives (64% vs. 81%, $p < 0.05$; RR 2.0). Cox et al. [63] in their cohort, SLN

ITC prevalence 6.3% (151 patients), reported a non-SLN rate of 9.3%, again with a majority of macro-metastases. Interestingly, the OS of SLN ITC patients who did not undergo ALND was significantly less than those undergoing ALND ($p < 0.05$). However, the OS for SLN ITC did not differ from those who were node negative. There was 1 axillary LR in the 44 SLN ITC patients not undergoing ALND (2.3%), compared to 6 axillary LRs in the 2109 SLN-negative patients (0.3%). Interestingly, the anatomical location of MM/ITC within the SLN has emerged as an independent predictor of non-SLN involvement, with intra-nodal/parenchymal lesions being more strongly associated with non-SLN metastasis than sinusal/vessel lesions [25,64]. Further evidence in support of the clinical significance of SLN ITC has also been put forward by other authors [65-67].

## Discussion

The last two decades have seen a paradigm shift, driven by improved understanding of the natural history of BC. Late presentation, delayed diagnosis and radical ablative surgery have been replaced by national screening, prompt diagnosis, breast conservation and rational axillary intervention. The ‘mechanistic’ model hypothesising centrifugal spread, justified the type of surgery advocated by Halsted [68]. More recently, the ‘biological’ model considers BC as a systemic entity at the time of diagnosis, where the behavior of disseminated small-volume disease determines prognosis [69,70]. Hence, modern surgical intervention aims to achieve local control, reduce morbidity and provide material for staging, without aspiring to eradicate all disease. Patients are pragmatically categorized as ‘good’ or ‘poor’

prognosis and their risk of local or distant failure justifies adjuvant local or systemic treatments targeting systemic small-volume disease and improving survival. Indications for local and/or systemic therapies have progressed, from simply considering axillary lymph node 'status', to integrating the absolute number of involved nodes, to contemporary deliberations regarding the tumour burden of individual nodes. Indeed, advances in sample processing and molecular biology continue to increase the likelihood of finding ITC, which currently represent the smallest detectable SLN lesions. Interestingly, the increasing frequency of small-volume lesions results from up-staging conventionally N0 disease, rather than down-staging N1 disease [3]. Paradoxically, women diagnosed with earlier/smaller primary tumours as a result of screening and improved diagnostic imaging, exhibit a trend for the apparent stage at diagnosis to be inadvertently increased by improved SLN analysis, illustrated in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database. Weaver [9] summarizes the potential impact of this iatrogenic stage migration as a ‘Will Rogers Phenomenon’; the prognosis of the node-negative category improves once the ITC are excluded, simultaneously the prognosis of the node-positive category improves once the ITC are included.

Caution is required to avoid the ‘catastrophic success’ resulting from increased diagnosis and potential for over-treatment of SLN ITC. Predicting the risk for non-SLN metastases in patients with SLN ITC is of paramount importance. The reasons why non-SLNs may harbour lesions larger their corresponding SLNs remain elusive. Prospective studies are required to determine whether removing an SLN with ITC constitutes adequate local control and enables ALND to be safely omitted. The results of current studies advocating a conservative approach may be confounded by limited

sample size, duration of follow-up, selection of low-risk patients, or the effects of adjuvant RT and systemic treatment [53]. Whilst the majority of patients with SLN ITC will not benefit from axillary treatment, these can not be reliably identified. Since SLN ITC are frequently confirmed following complete pathological assessment, any further surgery would need to occur on another occasion. Alternatively, axillary RT could be offered and there is evidence supporting the management of clinically node negative patients with axillary RT only. A study with 15 years follow-up has found no difference in survival between clinically node negative women with early breast cancer managed with ALND or axillary RT; although a slightly higher rate of axillary recurrence was noted [71]. However, this may be an equitable compromise, with ITC posing a lower risk of axillary LR than macro-metastasis and women spared the morbidity of ALND. On the other hand, many studies report appreciable rates of non-SLN macro-metastases in patients with SLN ITC. The added value of axillary treatment in patients with SLN ITC, in terms of local or distant failure, will therefore need to be determined by appropriately powered studies. The substantial reduction in the frequency of ALND and axillary RT over the last decade is supported by a large evidence base. Paradoxically, improved detection of minimal volume SLN lesions result in a steady 'creep' away from conventional nodal-negativity. Such inadvertent up-staging has the potential to drive management back towards historical over-treatment of the axilla. Therefore any change in practice necessitates level-1 evidence. Current American Society of Clinical Oncology (ASCO) practice guidelines state that ALND should be recommended for MM (N1mi) and state that the significance of ITC [N0(i+)] is currently unknown [13]. These patients have been assigned to the N0 group for staging and treatment purposes because "the unknown benefits of providing treatment for these small lesions would not overweigh the morbidity caused by the

treatment itself" [72,73]. Hence, despite the fact that several studies have found no difference between ITC and MM in terms of their predictive value for non-SLN macro-metastasis, management distinctions have been drawn and a watchful-waiting policy appears to be currently advocated. Clinical decisions regarding ALND or axillary RT remain best informed by integrating factors known to influence non-SLN positivity: including tumour size, lymphovascular invasion, number of SLNs examined and number of positive SLNs [29,30,44,74-77].

SLN ITC perhaps pose the greatest clinical dilemma in those without existing indications for adjuvant local or systemic therapy. A substantial proportion of non-SLNs harbour macro-metastases, potentially qualifying patients for adjuvant local therapies (including post-mastectomy RT) and/or systemic therapies. Avoiding ALND would prevent detection, resulting in under-treatment [53]. In several studies, SLN ITC are associated with an increased likelihood of systemic adjuvant therapy, the utility of which is not established. Decisions regarding adjuvant systemic therapy should therefore only be informed by established parameters. Indeed, current practice patterns have reduced the necessity for quantifying axillary disease, with decisions informed by patient factors and primary tumour characteristics [48]. Many node-negative patients receive combination therapy based on young age and primary tumour characteristics. Hormone receptor positive elderly patients, regardless of nodal positivity, often receive endocrine treatment rather than chemotherapy [48].

Although some studies report no associations, others demonstrate SLN ITC to be indicators of poor prognosis, associated with non-SLN involvement, LR and distant disease. Whilst these lesions can not simply be ignored, controversy surrounds

management decisions, regarding ALND, chest wall or axillary RT and systemic adjuvant treatment. Hence, reliably distinguishing ITC from MM remains important as this appears to categorize patient management into node-negative and node-positive status respectively [11,40,41,78]. Cserni [40,41] states that introduction of the ITC category potentially avoids stage migration, encompasses possible artefacts of passive tumour cell transport to the SLNs and may reduce over-treatment of low-volume nodal involvement [40,41]. In order to distinguish clinically relevant lesions, the current 'low-volume' classification system may need refining to include cell morphology, cell-cell/stroma interactions, anatomical location within the SLN and molecular profiling [25,56,79,80]. As HES is increasingly complemented by IHC and molecular analysis, subgroups will be identified in which ITC 'positivity' is modality dependent and reflected within classification systems [72]. Indeed, more than one entity of is likely to be included under the current umbrella definition of ‘no greater than 0.2 mm’. The quest remains to quantify a biologically relevant cut-off point for minimal SLN disease, below which patients are considered node-negative and further treatment safely omitted without detriment and above which the risks of axillary treatment and adjuvant systemic therapy are justified. Rather than working forwards from empirical and relatively arbitrary thresholds, a pragmatic approach should consider SLN tumour burden as a continuous variable and work backwards from what is clinically relevant to establish an evidence based micro-staging classification [75]. Indeed, the current distinction between ITC and MM seems to have little significance in predicting non-SLN involvement or prognosis [29,57,58,61].

The phenomenon of ITC is not unique to the lymphatic system or axillary nodes. ITC have been demonstrated in the circulation and bone marrow of BC patients using

sensitive immuno-cytochemical or molecular assays [81]. Their clinical relevance has yet to be determined, though reports suggest an association with poor prognosis [82]. Interestingly, bone marrow ITC are not associated with lymph node disease, implying independent micro-metastatic dissemination [83]. In keeping with concepts popularized by Fisher [69,70], the fundamental question then arises as to why we should treat small-volume axillary disease differently. It would seem rational to rely on systemic adjuvant treatments to perform in the axilla as they do elsewhere.

Randomised controlled trials are required to clarify the optimal management of patients with SLN ITC. It appears unlikely that determination of tumour burden alone will be sufficient to reliably guide clinical decisions regarding ALND, chest wall or axillary RT and systemic adjuvant treatment. Current prospective studies include the American College of Surgeons Oncology Group (ACOSOG) Z-0010 and Z-0011, which will investigate the survival of SLN positive patients who undergo ALND or observation (Z-0011) [84,85]. Z-0011 will determine whether removal of axillary nodes, which contain tumour, contributes to survival or whether it is just a staging procedure. If the SLN is negative, women will be enrolled in ACOS-OG ZOO10 to address the importance of occult small volume disease, evaluating the prognostic significance of lesions found only by SLN IHC in patients who undergo no further axillary treatment. In the European 2301 IBCSG trial MM are addressed in particular, with patients undergoing ALND or observation. Post-operative IHC analysis will identify some additional patients with ITC whose long term follow-up with regard to local and distant relapse will be of particular interest.

## Conclusions & Recommendations for Practice

The clinical relevance of ITC within the SLN should be primarily determined by the magnitude of their impact on patient management and outcome measures and not merely upon the presence of statistical significance. The modest up-staging within current classification systems is justified and reflects the marginally poorer prognosis for women with SLN ITC. Although, these patients differ from those without SLN ITC, management need not be altered where further axillary treatment with ALND or RT and systemic adjuvant treatment are already indicated. However, in the absence of level-1 guidance, each case requires discussion with regard to tumour and patient parameters in the context of the multidisciplinary team. Whilst there may exist a minimum SLN tumour burden for which further treatment can be safely omitted, this critical amount has yet to be defined. ITC identification remains dependent on analytical techniques 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 detection is unlikely unless they are employed. Evidence supporting the routine analysis of deeper tissue sections by IHC is lacking and molecular technologies should be restricted to research purposes at present. If the outcomes for current trials do not provide authoritative guidance, they may at least provide ethical and clinical justification for further studies to determine optimal management of each category of SLN tumour burden.

**Conflicts of Interest:**

None Declared.

**Authors' Contributions:**

NP Literature Review, Data Interpretation, Manuscript Writing & Editing

KM Study Concept, Manuscript Editing, Senior Author and Lean Clinician

**Abbreviations:**

Breast cancer (BC), axillary lymph node dissection (ALND), sentinel lymph node biopsy (SLNB), isolated tumour cells (ITC), sentinel lymph nodes (SLN), immunohistochemical (IHC), radiotherapy (RT), local recurrence (LR), micro-metastasis (MM), American Joint Committee on Cancer (AJCC), pathological tumour node metastasis (pTNM), haematoxylin and eosin staining (HES), reverse transcriptase polymerase chain reaction (RT-PCR), one-step nucleic acid amplification (OSNA), transcription-reverse transcription concerted reaction (TRC), carcinoembryonic antigen (CEA), European Working Group for Breast Screening Pathology (EWGBSP), recurrence free survival (RFS), overall survival (OS), disease free survival (DFS), Surveillance, Epidemiology and End Results (SEER), American Society of Clinical Oncology (ASCO), American College of Surgeons Oncology Group (ACOSOG).

**Figure 1**

Isolated tumour cells within a sentinel lymph node, haematoxylin and eosin stained.

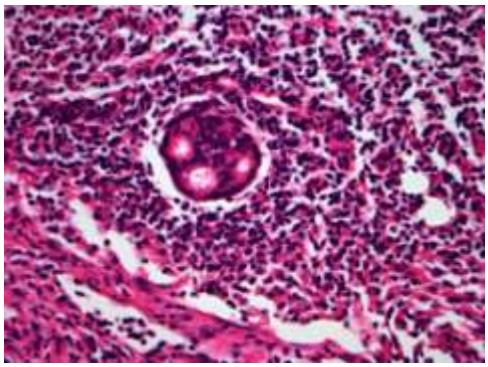


**Figure 2**

Isolated tumour cells within a sentinel lymph node, detected with cytokeratin immuno-histochemistry.

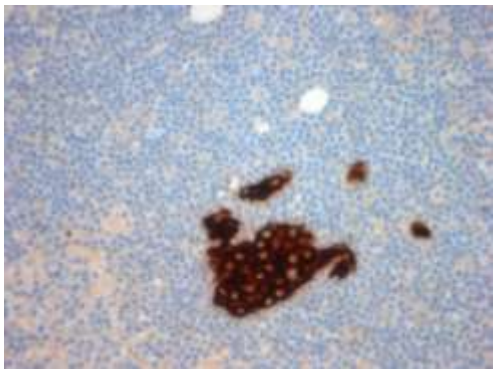
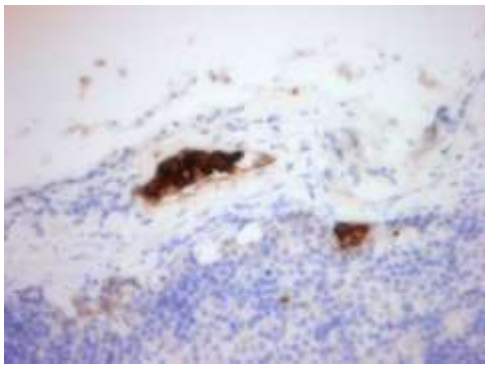


**Figure 3**

Sub-capsular isolated tumour cells within a sentinel lymph node, detected with cytokeratin immuno-histochemistry.



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