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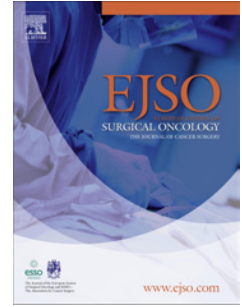
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Axillary nodal yields: a comparison between primary clearance and completion clearance after sentinel lymph node biopsy in the management of breast cancer

A Chakravorty , N Sanmugalingam, A Shrestha , E Thomee, J Rusby,
N Roche , F MacNeill

Academic Surgical Unit , The Royal Marsden Hospital, London, UK

Abstract

Aims : Axillary nodal status is the most important prognostic indicator which in turn influences adjuvant therapy and long term outcomes. The aim of this study was to compare total nodal yields from primary axillary lymph node dissection (pALND) with completion ALND after a cancer positive SLNB: either concurrently (cALND) following intra-operative assessment (IOA) of the SLN's or as a delayed procedure (dALND) when the SLN was found to be cancer positive on post operative histological examination.

Methods: All axillary procedures performed between May 2006 and September 2009 were identified from a prospective database and categorised into four groups : SLNB with no further axillary surgery, pALND, cALND and dALND. Total nodal yield was the sum of SLN/s and ALND yields.

Results: Of 1025 axillary procedures, ALND accounted for 332 (32.4%) of which 207 (62.3%) underwent pALND, 43 (12.9%) cALND , and 82 (24.6%) dALND . Median nodal yields were 15.0, 16.0 and 14.5 respectively (p = 0.3).

Conclusion: Total nodal yields for primary, concurrent and delayed ALND were comparable suggesting completion dALND performed as a second operation does not compromise axillary staging.

Keywords : Sentinel node biopsy, Intra-operative assessment, Breast cancer, Nodal yield

This study has been presented in the British Association of Surgical Oncology meeting 2009 in the Allan Edward prize section for oral presentations.

INTRODUCTION :

In the management of breast cancer, axillary node status is the most important prognostic factor and is a guide to adjuvant treatment. Sentinel lymph node biopsy (SLNB) is the recommended axillary staging procedure for early breast cancer [1] with axillary lymph node dissection (ALND) being reserved for patients with proven axillary metastasis either on pre-operative staging or SLNB. The 2009 UK Association of Breast Surgery (ABS) guidelines recommend, a positive axillary SLN is followed by further axillary treatment (2). More specifically, an ASCO 2005 statement advise completion ALND as do the more recent 2009 NICE guidelines with the aim of ascertaining total nodal burden and accurate prognosis [1,3].

A completion ALND can be performed concurrently (cALND) after IOA of the SLN under the same general anaesthetic, or as a second/delayed procedure (dALND) after post-operative histological SLN examination. Technically pALND and cALND are comparable but dALND is likely to be more challenging due to post SLNB healing process. The subsequent inflammatory changes, scarring and loss of tissue planes have the potential to limit the completeness of dALND with the theoretical risk of residual disease which may, in turn, translate to higher axillary recurrence rates. In addition, failure to remove all diseased nodes will reduce the total nodal burden, an important prognostic determinant. Such axillary under-staging may result in less optimal adjuvant therapy which may also influence local distant relapse rates.

Increasing use of SLNB has resulted in a rise of second surgical procedures for completion ALND [4]. The UK National health service breast screening programme (NHSBSP) audit from 2008-9 [5] documents the use of SLNB for 58% of screen detected cancers and of the 22% found to be node positive, just under a third had a second axillary procedure.

The global benefits of SLNB are reduced if a second operation is required so in an effort to limit additional surgery, we introduced IOA with touch imprint cytology (TIC) to allow cALND at the

time of SLNB. Our early TIC sensitivity of 67% was quite good[6] but TIC access was variable, dependant on pathologist availability and TIC sensitivity has declined in parallel with the increasing use of pre-operative axillary assessment. Axillary assessment involved pre-selection of the more obvious node positive axilla for pALND using ultrasound imaging with fine needle aspiration cytology (FNAC)/core biopsy of any suspicious nodes. Consequently although more node positive patients were identified pre-operatively for pALND, our dALND rate was rising as a result of TIC false negatives.

In view of the technical challenges posed by dALND, we wanted to determine lymph node yields for primary, concurrent and delayed ALND to establish any potential impact on cancer staging.

METHODS:

Following appropriate institutional approval we identified all axillary procedures carried out by three experienced breast surgeons and their teams between May 2006 and September 2009 from a prospectively collected database (electronic patient records). Four groups were identified – pALND , SLNB +/- IOA with no further axillary surgery, SLNB + IOA with cALND and SLNB +/- IOA with dALND. SLNB with no further axillary surgery was not included in the comparative analysis. SLNB was offered to all new breast cancer patients when the axilla was clinically and imaging/cytology negative. Primary ALND (level 2 & 3) was offered for proven nodal disease on pre-operative axillary ultrasound with positive cytology or offered if there was a high risk of nodal disease as determined by tumor size and /or histological characteristics combined with other risk factors / co-morbidities that might contraindicate two operative procedures. Exclusion criteria were referrals from other breast units post SLNB, neo-adjuvant chemotherapy treatment and those who declined dALND after positive SLNB. Completion ALND was offered for both micrometastatic and macrometastatic positive SLN's to determine total nodal disease burden. Number of nodes obtained were recorded from the electronic histopathology database and

cross referenced with the electronic operation notes. Total nodal yield was the sum of SLN's and ALND yield. Other potentially confounding variables such as primary tumor characteristics, operating surgeon and time to dALND were recorded to establish whether nodal yield was dependent on these variables.

SLNB was performed using UK standardised dual technique of isotope (Tc-99m labeled nano-colloid) and patent V blue dye. Intra-operative assessment (IOA) using touch imprint cytology (TIC) was introduced in late 2006 : the SLN's were bivalved along their long axis and imprinted directly on to coated microscopic slides and examined. Indeterminate (C3) or suspicious (C4) results were considered as negative results. Our methodology and early results of IOA have been published [6].

The statistical package was SPSS with the Kruskal-Wallis test looking for statistical significance between nodal yields of the three ALND groups. Confounding variables were investigated using univariate analysis to identify any association between these variables on the nodal yield in the node positive patients.

RESULTS

Nodal Yield

In the study period, 1025 axillary procedures for invasive breast cancer were performed of which 332 (32.4%) underwent ALND. Of these 207 had pALND, 43 cALND, and 82 dALND.

Patient Group	Delayed ALND	Concurrent ALND (SLNB + IOA)	Primary ALND
Total Patients = 1025	448	370	207
Node Positive	82	43	161

Table 1 : Distribution of patients who had axillary surgery in the three defined groups

The dALND group comprised of 21 who had a false negative TIC and 61 for whom IOA was not available but were positive on post-operative histology. Median nodal yields after primary, concurrent and delayed ALND were 15.0, 16.0 and 14.5 respectively which was statistically not significant ($p = 0.3$).

Patient Group	Delayed ALND (n = 82)	Concurrent ALND (n = 43)	Primary ALND (n = 207)	p value
Node Positive	82	43	161	
Median Nodal yield range	14.5 (5 – 34)	16.0 (7 – 38)	15.0 (4 – 38)	P = 0.3
Further positive nodes	22 (27 %)	15 (35%)	N/A	P =0.4
ALND with < 10 nodes	11 (14 %)	7 (16 %)	32 (15 %)	P = 0.5

Table 2: Comparison of nodal yield following ALND in the three groups

Node Positivity

207 of 1025 axillary procedures were pALND, of which 161 were node positive with a mean of 4.1 positive nodes. For completion ALND's (cALND and dALND) further nodal disease was found in 37 patients with a mean number of positive nodes was 1.5.

Adequacy of ALND

An adequate ALND was defined as a minimum total nodal yield of 10 nodes. Fewer than 10 nodes were obtained in 15% of pALND (CI : 7 -23), 16% of cALND (CI: 3-31) and 14% of dALND (CI: 12-23) and this was not statistically significant ($p =0.5$).

Uni-variate analysis was performed on the dALND group to evaluate other factors that might have influenced nodal yield. All dALND's were performed by supervised senior trainees, independently operating clinical fellows or consultant breast surgeons and no difference was noted in either the total axillary nodal yield (mean : Consultant 16.1, Senior trainee/fellow 14.0; $p=0.2$) or in the final number of positive nodes (mean : Consultant 3.0, Senior trainee/fellow 1.6; $p=0.2$). No relationship was found between number of days from SLNB to dALND for either the total nodal yield ($p=0.8$) or final number of positive nodes ($p=0.7$). The median interval between primary and delayed surgery was 24 days (7-196), the wide range is accounted for by some node positive patients proceeding to chemotherapy prior to dALND.

A trend for declining nodal yield with increasing age was noted which was of marginal statistical significance as shown in Table 3.

Nodal Yield	Mean Age	p value
≥ 10 nodes	56 years (95% CI : 54-58)	$p= 0.05$
< 10 nodes	63 years (95 % CI : 57-69)	

Table 3: Univariate analysis showing effect of age on nodal yield

DISCUSSION

ALND can now only be justified in node positive patients as SLNB can accurately discriminate between node positive and negative patients [7,8] and has equivalent survival and loco-regional recurrence rates with significantly lower morbidity than ALND[9].

Up to 30% of node positive patients can be identified pre-operatively with imaging and FNAC/core biopsy [10] – the remaining node positive patients are then detected by SLNB.

However, if the SLN is positive, further axillary treatment is recommended. ABS guidelines recommend completion ALND, axillary radiotherapy or entry into trial [2,3]. We offer completion ALND to maximize prognostic information by ascertaining total nodal disease burden. Total nodal disease burden is particularly useful in determining the need for post mastectomy radiotherapy or entry into SUPREMO the UK post mastectomy chest wall radiotherapy trial.

For a variety of reasons a completion ALND after a positive SLNB is performed as a delayed procedure so it remains important to determine if total nodal yield for dALND is comparable to that for pALND.

These results demonstrate comparable nodal yields for ALND performed either as a primary procedure, concurrent with SLNB if IOA was available, or if not as a second operation. These findings are important as they indicate that regardless of the technical challenges posed by dALND the quality of axillary staging and therefore appropriateness of adjuvant treatment can be maintained.

Our results are supported by other smaller studies, Braems et al [11] in a retrospective study found no difference in lymph node yield between pALND without previous SLN biopsy and patients with SLN biopsy followed by dALND. However, the study did not compare the nodal yield in the concurrent group. Byrne et al [12] in their study discussed the timing of axillary lymph node dissection and concluded that immediate ALND has many advantages.

Intra-operative assessment and concurrent ALND

When IOA was available, just under 70% of node positive patients were spared a second axillary operation. The proportion of SLN positive patients who have IOA with cALND is difficult to ascertain nationally but a recent survey revealed only 20 % of UK breast units have access to IOA [13] and recent data from the 2008-9 NHSBSP audit demonstrates second operation rates are increasing as SLNB is implemented across the UK [5] supporting the survey findings that

IOA is not widely available. Even if available, IOA it may not be adopted: it is time consuming, expensive, and adds to the complexity of pre-operative consenting. In addition if ALND is required, it disrupts planned operative and inpatient scheduling. Furthermore, if only 30% of SLNB positive patients have further nodal disease on completion ALND, patients may prefer to be more actively involved in the decision making regarding the necessity of a completion ALND rather than consenting pre operatively to proceed to cALND if the SLN is positive. Newer molecular SLN assays can quantify SLN disease burden which may allow a more targeted approach to cALND [14].

Determinants of nodal yield and adequacy of node retrieval

Axillary nodal yields are not just surgeon dependent but also rely on a careful and thorough pathological analysis of scarred and sometimes fragmented dALND tissue.

Nodal yield is a surrogate marker for quality of the accuracy of ALND as a staging procedure and of the completeness of ALND when used for therapeutic purposes: yields of over 10 nodes are accepted as indicating an adequate dissection [15]. It is reassuring to establish that, despite a heavy nodal burden in the pALND group, nodal yield is unaffected. However, 16% of pALND patients had potentially inadequate axillary staging and axillary treatment. As with our study other groups have found that increasing age correlates with lower nodal yield [11]. A plausible explanation for this finding could be surgical pragmatism: older patients are less likely to benefit from potentially small survival advantages conferred by extended ALND whereas the morbidity may have significant functional implications.

Level of ALND

Equivalent nodal yields between the pALND and the completion ALND groups suggest that surgeons perform a standard ALND for all patients. However, if further disease is found in less than 50% of completion ALND [16] it is important to limit the morbidity associated with level 3

ALND. This is further reinforced by our series, where preoperative axillary ultrasound and cytology is standard, only 30 % of the completion ALND group had further nodal disease. High nodal yields may be appropriate for those who have further nodal disease, but less so for the 50 - 70% of patients who had no further disease as they will experience the same surgical morbidity for very little benefit. The decreasing likelihood of further nodal disease after a positive SLN suggests we should re-evaluate the extent of completion ALND. Indeed recent a ASCO presentation of the Z0011 study has questioned the need for completion ALND in early stage breast cancer [17].

Our study does not address complications or morbidity of dALND but large multi-centre trials have shown that long term complications such as lymphoedema and pain are not increased by two surgical procedures and are similar after pALND and completion ALND [18,19] .

CONCLUSION

In the UK widespread uptake of SLNB but restricted access to IOA means that dALND is the standard management for a positive SLN. Our data demonstrates there is no difference in the mean nodal yield or adequacy of ALND between pALND, cALND and dALND indicating that despite the technical challenges posed by delayed axillary surgery for both the surgeon and pathologist, nodal yields can be maintained. Comparable nodal yields indicate that axillary staging and treatment has not been compromised by an interval between primary and secondary ALND.

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LEGEND 1

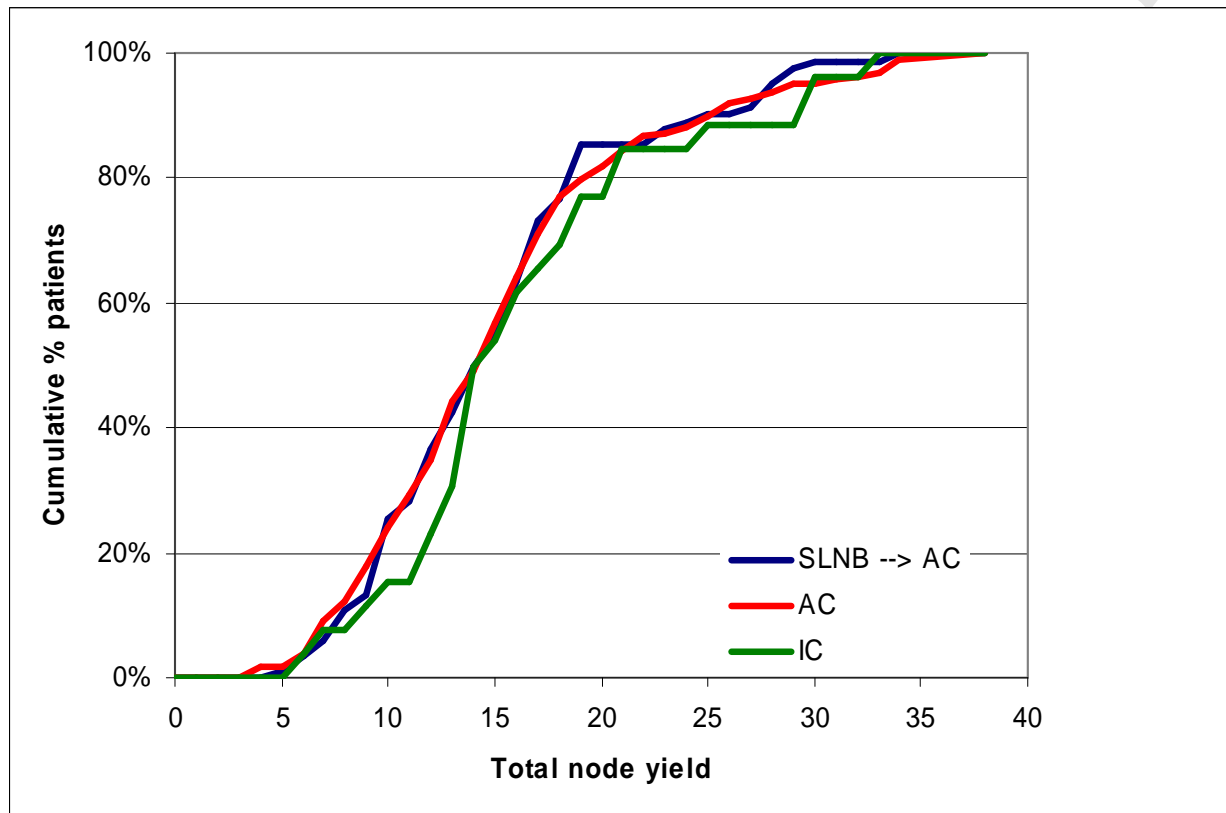


Figure 1 : Comparison of total nodal yield following axillary dissection

This graph shows no statistically significant difference in the total axillary nodal yield for cALND (IC), pALND (AC) and dALND ($p=0.3$; Kruskal-Wallis).