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Axillary Nodal Examination in Breast Cancer: How Much Is Enough? Evidence for a New Minimum

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ABSTRACT

Background: Axillary nodal spread is an established prognostic factor in breast cancer. Axillary nodal dissection and subsequent pathological examination is considered the gold standard technique of assessing the axilla for metastatic disease. A minimum of ten level I axillary nodes are required to be examined before an axillary specimen can be reliably labeled as disease free. This recommendation is based on a mathematical prediction model and such methodology has certain inherent limitations. In this study, we sought to revisit this concept of minimum nodes required to deem an axilla as true negative by using a linear correlation model.

Methods: Medical records of 165 consecutive breast cancer patients attending a medical oncology department for adjuvant therapy were assessed for inclusion. One hundred and forty-five breast cancer patients in clinical stages I-III met the inclusion criteria. Patients referred after neoadjuvant chemotherapy, breast conservation surgery, palliative mastectomy, and mastectomy for metastatic disease were excluded from the study. The study samples were segregated into groups of 1-5, 6-10, 11-15, 16-20, 21-25, and more than 25 nodes. A linear regression model was used to assess the association between the nodal positivity and nodal groups. The spearman rho with P value was calculated for the model. Factors influencing the nodal yield of an axillary specimen were selected from the published literature and the same variables were evaluated in the study cohort.

Results: A total of 1882 nodes were harvested from 145 axillary specimens and 320 nodes were positive for metastatic disease. The mean nodal harvest per axillary specimen was 11 nodes. The linear correlation model evaluating the association between nodal positivity and total nodal yield showed a spearman correlation coefficient of Rho = - 0.82 with P=0.04. To avoid bias due to the uneven sample size, the nodal ratio was calculated for each group and the linear association model reapplied to test the association with the total nodal harvest. A spearman rho of R = -0.94 with P=0.004 was obtained. The nodal groups tested for significance showed P= 0.0001 for the group 1-15 nodes. Evaluation of the factors likely to influence nodal yield showed that age (P=0.15) and obesity (P=0.67) had no effect on the nodal harvest. Tumor stage (P<0.001) and operating surgeon (P=0.0001) had a significant effect on the total nodal harvest.

Conclusions: The recommendation of a minimum of ten axillary nodes to be examined to determine true negativity of an axillary specimen needs reassessment. A new minimum of fifteen nodes is suggested before an axillary specimen is reliably deemed free of metastatic disease.

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Introduction

Axillary nodal involvement is an established prognostic determinant in breast cancer. A direct association between axillary nodal involvement and survival was well documented by Fischer *et al.* who demonstrated a five-year survival of 82.3%, 73%, 45%, and 28% for node negative, 1-3, 4-12, and more

than 13 involved axillary nodes, respectively.[1] Axillary nodal dissection and subsequent pathological examination has been the gold standard technique of assessing the axilla for metastatic disease.[2] Traditionally, axillary dissection is performed with staging, therapeutic, and prognostic goals in the management of breast cancers. The oncological reliability of sentinel node biopsy coupled with the necessity to reduce the high arm morbidity associated with a standard axillary dissection prompted a paradigm shift in axillary management of early breast cancers. In contemporary practice, the staging role of an axillary dissection has been eclipsed by the sentinel node biopsy technique and completion axillary dissection and primary axillary dissection reserved for pathologically proven nodes in the axilla.[3] Despite these changes in management principles, many patients with node negative early breast cancer are still subjected to a staging axillary dissection as the sentinel node biopsy technique is available only in selected oncology centers in India.

Axillary nodal dissection results in the assignment of a pathological nodal category based on the number of involved nodes. The nodal positivity has been shown to vary with the number of nodes examined and it has been recommended that a minimum number of ten level I axillary nodes should be examined before an axillary specimen can be reliably deemed as free of metastatic disease.[4] It is important to note this recommendation is based on a mathe-matical model that predicts the probability of a false negative axilla in a T1 tumor when all 11 examined nodes are negative is 6.14% with 90% certainty. This prediction model was developed from a data set of 1446 patients from the national cancer institute in Milan.[4] To adopt this approach universally may be fundamentally flawed as the nodal yield and positivity have been shown to vary with multiple disease, patient, or surgeon related factors. Somner *et al.* suggested a minimum of 16 nodes to be examined to ensure a negative axilla.[5] In this study, we sought to revisit this concept of minimum nodes required to deem an axilla as reliably negative for regional disease spread.

Methods

Medical records of 165 consecutive breast cancer patients attending a medical oncology department for adjuvant therapy were assessed for inclusion. The patients with a core biopsy proven diagnosis of breast cancer in clinical stages I-III who were surgically treated with a modified radical mastectomy were included in the study. The patients who were referred after breast conservation surgery, palliative mastectomy, and mastectomy for metastatic disease were excluded from the study. Axillary dissection included dissection of level I, II, and III nodes. Neo adjuvant chemotherapy is known to influence both the nodal positivity and the yield; hence, preoperative chemotherapy was a strict exclusion criterion.

The study included 145 evaluable patients. Basic demographic and disease-related data were collected. The post-operative pathology report was the main source of study information. All operative specimens were dissected by the surgeon for axillary nodes before transportation to the pathology lab in 10% formalin solution. The specimens were re dissected after fat clearance by a pathologist to further enhance the nodal yield and the final number harvested for that specimen by the summation of the surgeon's and the pathologist's nodal harvest. All nodes in a specimen were microscopically examined, initially by a single transverse section through the long axis. No further examination was done for positive nodes (> 0.2mm deposit); however, further sectioning of negative nodes was done to ensure true negativity. Immunohistochemistry based techniques were not used in this study to confirm negative nodes. The total nodal yield, nodal positivity, and nodal ratio were determined for each study specimen. For the purpose of this study, nodal ratio was defined as the ratio of positive nodes to the total nodal harvest.

The study samples were segregated into groups of 1-5, 6-10, 11-15, 16-20, 21-25, and more than 25 nodes. A linear regression model was used to assess the association between the nodal positivity and nodal groups. The spearman rho with P value was calculated for the model. Factors affecting the nodal yield of an axillary specimen were selected from published literature and the variables (age, obesity, tumor stage, and operating surgeon) were evaluated in the study cohort.[6-8] Age and tumor stage were analyzed with a linear regression test. The operating surgeon was previously reported as a variable affecting the nodal yield. The study participants were segregated into two groups based on the surgery performed by surgical oncologists or by general surgeons. The impact of the surgeon on the total nodal yield of an axillary specimen was analyzed as a categorical variable using the chi-square test. A P value less than 0.05 was considered significant.

Results

The baseline characteristics of the study patients are given in Table 1. A total of 1882 nodes were harvested from 145 axillary specimens and 320 nodes were positive for metastatic disease. The mean nodal harvest per axillary specimen was 11 nodes. The correlation model evaluating the association between nodal positivity and total nodal yield showed a spearman correlation coefficient of Rho = -0.82 with P=0.04 indicating a strong reverse association between the two variables (Figure 1). As the sample size in individual nodal groups was unbalanced, the nodal ratio was calculated for each

group and the linear association model reapplied to test for an association with the total nodal harvest (Figure 2). A spearman rho of R = -0.94 with P=0.004 was noted, indicating a strong reverse association between the nodal positivity yield and the increase in nodal examination. The nodal positivity increased from the group 1-5 nodes with the highest nodal positivity achieved in the nodal group 6-10 nodes; there was a steady decline in the yield of positive nodes despite the increase in nodal examination thereafter. The nodal groups tested for significance showed P= 0.0001 for the group 1 -15 nodes. The factors likely to influence the nodal yield were evaluated; age (P=0.15) and obesity (P=0.67) had no association with the nodal harvest. Tumor stage (P<0.001) and operating surgeon (P=0.0001) had a significant effect on the total nodal harvest. The mean nodal harvest for surgical oncologists was 14 nodes compared to 8 nodes for non-oncology trained surgeons.

Table 1. Baseline characteristics of the study cohort

	N=145
Age (mean)	52.5 years
Menopausal status	
Pre	53 (36%)
Post	92 (64%)
Histology	
Infiltrative ductal –NOS	140 (96.55%)
Lobular	3 (2.06%)
Medullary	1 (0.68%)
Metaplastic	1 (0.68%)
Tumor stage	
T1	27 (18.6%)
T2	85 (58.6%)
T3	31 (21.3%)
T4	1 (0.68%)
Stage	
I	15 (10.5%)
II	78 (53.7%)
III	52 (35.8%)
Pathological nodal stage	
N1	70 (48.3%)
N2	53 (36.5%)
N3	22 (15.2%)
Operating surgeon	
Oncologist	96 (66.2%)
Non-oncologist	49 (33.8%)

Discussion

Axillary dissection has staging and prognostic applications in node negative early breast cancer. The sentinel node biopsy technique has replaced the axillary dissection as a staging procedure in clinically node negative early breast cancer; however, it is still required as a staging procedure when the sentinel node technique is unavailable or otherwise contraindicated. The axillary nodal harvest has been suggested as a surgical quality

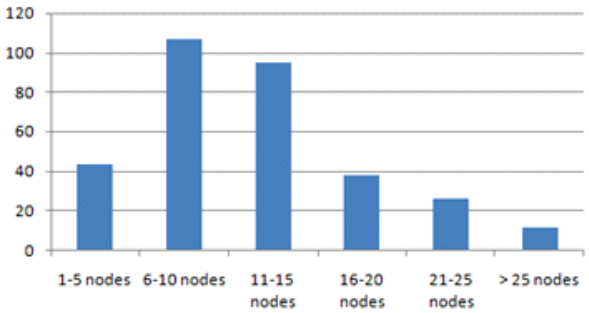

Figure 1. Relationship of nodal positivity with nodal groups

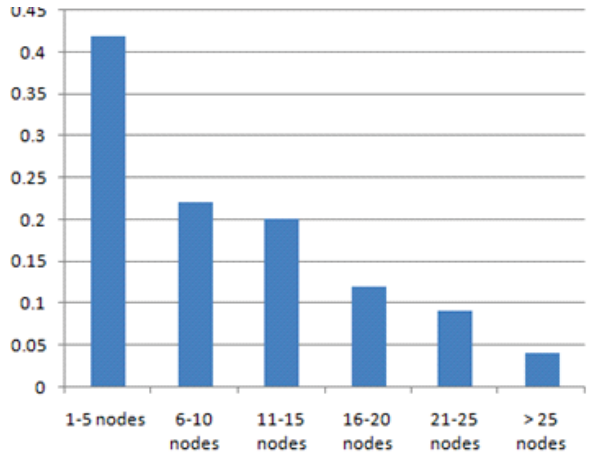

Figure 2. Relationship of nodal ratio with nodal groups

indicator. Pathological axillary staging requires a minimum of ten level I axillary nodes to be examined before a true negative axilla can be assumed. This criterion was determined based on a mathematical prediction model with data derived from patients treated between 1983 and 1986.[4] Our study suggests the minimum nodes required to be examined are 15.

Applying a linear correlation model, our study clearly showed that the nodal positivity declined with the increase in nodal examination (Rho= -0.82, P=0.04). The relationship was identical between the nodal ratio and the number of nodes examined (Rho=-0.94, P=0.004). A significant result (P=0.001) was obtained for nodal groups 1-15, indicating the nodal positivity rate does not increase significantly after examining 15 nodes. Somner *et al.* used an identical study methodology to evaluate 609 patients and suggested a minimum of 16 nodes to be examined to be confident of a disease negative axilla.[5] Blancas *et al.* conducted a study to determine whether the number of nodes removed at axillary dissection was associated with recurrence and concluded a minimum of 6 nodes was to be examined to be confident of a node negative status.[9] This study had 49% of the samples in T1 (< 20mm) category while the same (tumor size < 20mm) constituted only 18.6% of the samples in our study; as nodal positivity was significantly affected by the tumor size (P< 0.001), the noted differences could be explainable by more

samples with larger tumor sizes in our study. The Danish breast cancer cooperative group, based on the data of 31679 patients, reported that dissection of 20 nodes rather than 10-14 nodes increased the probability of nodal positivity by 7% for T1a, 9% for T1c, and 10% for T3 tumors.[10]

Several variables have been reported to influence the nodal yield of axillary dissection. Age and body mass index did not significantly affect the nodal yield in this study, which is in accordance with the results of a study reported by Lee *et al.*[11] Surgical training related factors (oncology vs. non-oncology) have been shown to alter nodal retrieval. This factor was a significant variable in our study (p=0.0001). In the present study, 34% of the axillary dissections were performed by non-oncologists and the mean nodal harvest for this group was 8 nodes. It is probable that this factor resulted in a lower mean nodal harvest observed in this study; but it is unlikely to have influenced the analysis of the primary study objective as a linear correlation model, and not to a probability based model, was used for assessing the minimum nodes required to deem an axilla negative for metastatic disease.

This study has a few limitations. The sample size was small and the dependent nature of the observations (lymph nodes) may be considered as a design limitation for the linear regression model. The minimum number of histological sections required to confirm a disease free nodal status was left to the pathologist's discretion and keratin immune histochemistry was not used in this study to confirm a true negative result. The nodal yield has been shown to vary with the pathologist examining the specimen; however, such data were unavailable due to the retrospective nature of this study. Survival and recurrence data (follow-up) were not incorporated into the study design to assess whether the new proposed minimum of 15 nodes translates to a clinical benefit.

This study demonstrates that the prevailing standard of a minimum of ten axillary nodes to be examined to assign pN0 category needs revision. A new minimum of fifteen nodes is suggested before an axillary specimen is reliably deemed free of metastatic disease. The implications on the cost, resources, and disease recurrence of this new recommendation remain unknown.

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