

# Predictors of axillary lymph node metastases in women with early breast cancer in Singapore

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## ABSTRACT

**Introduction:** The presence of axillary lymph node metastases is an important prognostic factor in breast cancer. Sentinel lymph node biopsy (SLNB) is an emerging method for the staging of the axilla. It is hoped that with SLNB, the morbidity from axillary lymph node dissection (ALND) can be avoided without compromising the staging and management of early breast cancer. However, only patients found to be SLNB negative benefit from this procedure, as those with positive SLNB may still require ALND. Our objective is to study the various clinico-pathological factors to find predictive factors for axillary lymph node involvement in early breast cancer. It is hoped that with these factors, we will be better able to identify groups of patients most likely to benefit from SLNB.

**Methods:** A retrospective study of 380 early breast cancer cases (stage T1 and T2, N0, N1, M0) in women treated in the Department of General Surgery, Tan Tock Seng Hospital, between January 1999 and August 2002, was conducted. Incidence of nodal metastases was correlated with clinico-pathological factors, and analysed by univariate and multivariate analyses.

**Results:** Approximately 35 percent of the 380 cases of early breast cancer had nodal metastases. Multivariate analyses revealed four independent predictors of node positivity: tumour size (p-value equals 0.0001), presence of lymphovascular invasion (p-value is less than 0.0001), tumours with histology other than invasive ductal or lobular carcinoma (p-value equals 0.04), and presence of progesterone receptors (p-value equals 0.05).

**Conclusion:** We have found independent pre-operative predictive factors in our local population for the presence of nodal metastases. This information can aid patient selection for SLNB and improve patient counselling.

**Keywords:** axillary lymph node, breast cancer, node dissection, sentinel lymph node biopsy

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## INTRODUCTION

The presence of axillary lymph node metastases is an important predictor of survival in patients with infiltrative breast cancer<sup>(1,2)</sup>. It also determines the need for adjuvant chemotherapy and/or hormonal therapy. Axillary lymph node biopsy (ALNB) remains the best way to evaluate the presence of node metastases. It is also important in loco-regional disease control. However, it is associated with complications such as lymphoedema, shoulder stiffness, breast oedema, seroma formation, upper limb numbness and brachial plexopathy<sup>(3,4)</sup>.

Sentinel lymph node biopsy (SLNB) is the emerging minimally-invasive alternative to ALNB, avoiding the complications of the latter. However, it is resource-intensive and is only beneficial in node negative patients, as node positive patients will still require ALNB. The aim of this study is to define whether any preoperative factors could help predict patients who are likely to be node-negative and thus most likely to benefit from SLNB.

## METHODS

The clinical, operative and pathological data for all breast cancer patients undergoing breast cancer surgery at the Department of General Surgery, Tan Tock Seng Hospital was collected weekly by a breast cancer nurse, and collated into a breast cancer database. We retrospectively reviewed all cases in this database between January 1999 and August 2002, further evaluating all 380 who met our inclusion criteria of early breast cancer (AJCC 5th edition Stage T1 and T2,N0, N1, M0). Breast cancer patients seen in our institution but who did not receive surgery were not included in this study.

Clinical factors assessed were: age at diagnosis, race, parity, menopausal status and family history of breast cancer (any female relative with positive history

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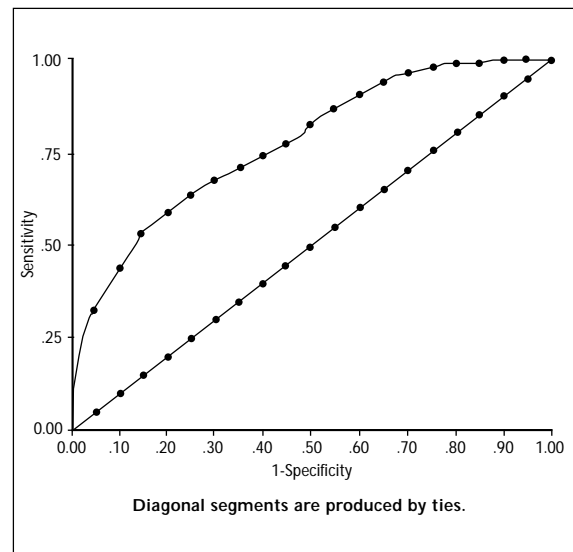
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**Table I. Patient characteristics (380 breast cancers in 373 patients).**

Variable	Number	%
<b>Race</b>		
Chinese	321/373	86.1
Malay	30/373	8.0
Indian	15/373	4.0
Others	7/373	1.9
<b>Age (in years)</b>		
≤35	13	3.5
36-50	149	39.9
51-75	189	50.7
>75	22	5.9
<b>Menstrual status</b>		
Premenopausal	154	41.4
Postmenopausal	218	58.6
Not documented	1	
<b>Tumour stage</b>		
T1a	23/380	6.3
T1b	37/380	9.6
T1c	163/380	43.0
T2	157	41.1
<b>Grade</b>		
1	81/380	21.3
2	198/380	52.1
3	101/380	26.6
<b>Histology</b>		
Invasive ductal	321	84.5
Invasive lobular	13	3.4
Others	46	12.1
<b>Nodal status</b>		
Positive	136	35.8
Negative	244	64.2
<b>Lymphovascular invasion</b>		
Positive	57/374	15.2
Negative	317/374	84.8
Unknown	6	
<b>Oestrogen receptor</b>		
Positive	244/358	68.2
Negative	114/358	31.8
Unknown	22	
<b>Progesterone receptor</b>		
Positive	158/356	44.4
Negative	198/356	55.6
Unknown	24	

of breast cancer). Pathological factors evaluated were: primary tumour size (maximum diameter of the invasive component or the largest invasive component if multiple foci of invasion were present) measured microscopically; grade (modified Bloom and Richardson system); histology; lymphovascular invasion (tumour cell emboli within endothelium-lined vascular spaces seen on Haematoxylin and Eosin stained slides of

**Fig. 1** ROC analysis.

Area under curve = 0.77 ( $p < 0.001$ ).

the breast cancer) and progesterone and oestrogen receptor status (studied by immunohistochemical analyses and recorded as negative or positive). All patients had at least level II ALNB with an average of 14 lymph nodes removed and the pathological status was known.

Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) version 10.0 (Chicago, IL, USA). Besides simple cross tabulations, simple logistic regression analyses were performed with presence of axillary lymph node metastases as the dependent variable. For multivariable analysis, forward stepwise multiple logistic regression was performed using all potential predictor variables, with a cut-off p-value of 0.05 used for model selection. To assess model fit, the Hosmer-Lemeshow test was used, and receiver operating characteristic (ROC) analysis was performed on the predicted log odds values. Patients with unknown factors were excluded from the analysis.

## RESULTS

The characteristics of the 380 cases (373 women, including seven with bilateral breast cancer) of early breast cancer treated in our centre are summarised in Table I. The median age of the subjects was 52 years, with a range from 24 to 87 years. Of the 380 subjects, 136 (35.8%) were found to be node positive. The median number of nodes examined was 14 (standard deviation [SD] = 6.81), with a range of 1-41. Table II shows the distribution of the 11 predictor variables with the proportion of subjects in each category with at least one lymph node positive for metastases and the odds ratios for

Table II. Univariable analysis.

Variable/description	Number of patients	Positive nodes (%)	OR	95% CI	p-value
<b>Age ( in years)</b>					0.79
0-35	13	38.5	Baseline		
36-50	151	37.7	0.97	0.30, 3.1	
51-75	194	35.1	0.86	0.27, 2.7	
75-87	22	27.3	0.60	0.14, 2.6	
<b>Race</b>					0.30
Chinese	328	35.4	Baseline		
Malay	30	36.7	0.90	0.41, 2.0	
Indian	15	53.3	2.1	0.73, 5.8	
Others	7	14.3	0.30	0.04, 2.5	
<b>Parity</b>					0.03
Nulliparous	83	26.2	Baseline		
Multiparous	290	39.0	1.77	1.03, 3.0	
<b>Menopausal status</b>					0.45
Premenopausal	156	38.5	Baseline		
Postmenopausal	223	33.6	0.85	0.56, 1.30	
<b>Family history</b>					0.40
Absent	348	36.5	Baseline		
Present	31	29.1	0.71	0.32, 1.59	
<b>Tumour stage</b>					<0.0001
1a	23	4.3	0.04	0.005, 0.30	
1b	37	18.9	0.17	0.067, 0.43	
1c	163	27.6	0.33	0.21, 0.53	
2	157	52.9	Baseline		
<b>Tumour grade</b>					0.0003
1	81	21.0	Baseline		
2	198	34.3	1.79	0.98, 3.3	
3	101	50.5	3.6	1.86, 6.9	
<b>Tumour histology</b>					0.0003
Invasive ductal	322	39.6	Baseline		
Invasive lobular	13	30.8	0.68	0.21, 2.3	
Others	45	10.9	0.19	0.07, 0.50	
<b>Lymphovascular invasion</b>					<0.0001
Absent	317	28.7	Baseline		
Present	57	75.4	8.5	4.4, 16.5	
<b>Oestrogen receptor</b>					0.21
Absent	112	34.8	Baseline		
Present	236	38.6	1.37	0.83, 2.3	
<b>Progesterone receptor</b>					0.54
Absent	154	37.7	Baseline		
Present	193	37.8	1.16	0.73, 1.83	

OR: odds ratio; CI: confidence interval.

presence of axillary lymph node metastases and p-value derived from simple logistic regression.

There was a significant association ( $p < 0.05$ ) between parity, T-stage, tumour histology, grade and lymphovascular invasion with nodal status. The other variables listed in Table II show, in univariable analysis, no statistically significant association with nodal involvement. Multivariable logistic regression analyses revealed the following independently

significant variables: T-stage, tumour histology, lymphovascular invasion and progesterone receptor status (Table III). The model fits fairly well, as indicated by the Hosmer-Lemeshow test ( $p = 0.48$ ) (small p-values indicate lack of fit) and the ROC analysis (Fig. 1).

## DISCUSSION

ALNB remains the gold standard in determining prognosis, adjuvant therapy and loco-regional control.

However, as mammography screening for breast cancer becomes more prevalent, breast tumours are being found at smaller sizes than before. With this, the positive yield of axillary lymph node dissection also decreases. Node negative patients do not benefit from ALNB but may suffer its attendant complications. This has led to calls for more conservative management of the axilla in early breast cancer.

SLNB is a promising emerging alternative to a full ALNB. Many studies have validated its accuracy, although the long term effects of foregoing a full dissection remains unknown till large scale randomised controlled trials such as the NSABP-32 trial are completed<sup>(3)</sup>. One of the drawbacks of SLNB is that in the event there are lymph nodes positive for metastases, the patient will be required to undergo further surgery under general anaesthesia for the completion axillary clearance. In our study population, that would mean that 35% of our patients would need to go for a second surgery. However, we feel that by using a combination of factors that can be determined preoperatively, we can define subgroups of women who will be at a lower risk for lymph nodes positive for metastases.

There have been several studies looking into predictive factors for the presence of axillary lymph node metastases, however to our knowledge, this is the first local study on this important topic. Larger tumour size was found to be an independent predictor of node positive disease in our study, concurring with data from several other centres<sup>(5-9)</sup>.

Lauria et al (1995)<sup>(10)</sup> showed the prognostic value of lymphovascular invasion in operable breast cancer and its positive correlation with metastatic axillary lymph nodes, which is in agreement with our findings. It is well known that certain histological subtypes of breast cancer are associated with a better prognosis and lower rate of node metastases, but literature review did not reveal any other study where this was shown as an independent predictor of nodal status. This may be due to the fact that these favourable histological subtypes are also closely related to smaller tumour size, thus the difficulty in showing that the lower rate of lymph node metastases in these cancers is related to their histological type and not to the smaller tumour size. Our data also shows that histological subtypes with favourable prognosis such as tubular, colloid, medullary and cribriform tumours are associated with node negativity which approaches 100%. This was found to be statistically significant when compared to infiltrative ductal carcinoma and is independent of the tumour size.

While there have been several papers<sup>(5,7,9)</sup> that have not shown progesterone receptors as useful

**Table III. Multivariable analysis (final model).**

Variable/description	OR	95% CI	p-value
<b>Tumour stage</b>			0.0001
1a	0.06	0.007, 0.50	
1b	0.18	0.065, 0.49	
1c	0.38	0.22, 0.67	
2	Baseline		
<b>Tumour histology</b>			0.04
Invasive ductal	Baseline		
Invasive lobular	0.90	0.24, 3.4	
Others	0.26	0.09, 0.72	
<b>Lymphovascular invasion</b>			<0.0001
Absent	Baseline		
Present	7.7	3.5, 17	
<b>Progesterone receptor</b>			0.05
Absent	Baseline		
Present	1.8	1.0, 3.0	

Hosmer and Lemeshow Goodness-of-Fit Test (8 groups): p=0.48.

OD: odds ratio; CI: confidence interval.

predictors of axillary lymph node metastases, a recent study by Viale et al<sup>(11)</sup> of 4,351 patients who underwent SLNB, showed that the prevalence of SLN metastases had an inverse relationship with a lack of progesterone receptors. Statistical issues, such as variations in modeling procedure in small to moderate size data-sets between the different studies, could be an explanation for this. We feel that the relationship between PR receptors and lymph node status warrants further study.

Tumour size, histological type, presence of lymphovascular invasion and PR status can be determined pre-operatively with the combination of imaging and trucut biopsies. We acknowledge that our findings are based on retrospective analysis of post-operative data, and that a prospective study will be needed to confirm them. We hope to use this additional information to predict the possibility of nodal metastases in an individual patient. This will improve pre-operative assessment and planning, and aid with better pre-operative counselling.

Olivotto et al (1998)<sup>(8)</sup> used their predictors to develop a three-variable model to classify patients into various groups based on their risk of nodal involvement. Using their model, they identified subsets of patients who could safely avoid the morbidity of axillary dissection. If our data is confirmed on prospective study, we hope to develop our own model in the future to identify patients with the lowest risk of node metastases and thus most likely to benefit from SLNB.

In conclusion, we have found independent pre-operative predictive factors in the local population

for the presence of axillary lymph node metastases. Armed with this information, we can select women who are likely to be node negative, and give better pre-operative counselling with clearer information to patients regarding the chances of requiring further axillary dissection. This will further empower patients in the participation of the management of their disease, giving them a choice between going for an ALNB upfront or a SLNB, fully aware of the chances that they may require follow-up surgery.

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