Correlation of Various Biomarkers with Axillary Nodal Metastases: Can a Panel of Such Biomarkers Guide Selective Use of Axillary Surgery in T1 Breast Cancer?

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Abstract To evaluate the correlation of various clinicopathological variables with axillary nodal involvement in T1 breast cancer & to identify a sub-group of T1 cancers, on the basis of observed variables, with a low risk of axillary nodal metastases. Clinico-pathological variables observed included tumor size, lymphovascular invasion (LVI), histological grade of tumor, tumor palpability, estrogen/progesterone (ER/PR) & her2/neu receptors, age, family history, histological type of tumor, axillary nodal metastases for 100 patients without clinically palpable nodes who underwent axillary lymph node dissection in Bombay Hospital & Medical Research Center from March, 2009. Data compiled was analyzed by univariate & multivariate analysis. All the variables viz. tumor size, LVI, histological grade, tumor palpability & ER/PR/Her2 receptor profile, which were found to be significantly associated with axillary lymph node involvement (ALNI) on univariate analysis were also found to be independent predictors of ALNI on multivariate analysis. Age of the patient, family history & histological type of tumor were not significantly correlated with ALNI. None of the 12 patients with tumor biomarker profile of T1a-b tumors without LVI & with histological grade I, had ALNI. The risk of ALNI can be predicted by using various tumor biomarker variables. Based on the predicted risk of ALNI, the management strategy for axilla can be individualized. The omission of operative axillary staging may be considered in patients with low predictive risk of ALNI.

Keywords Breast · Cancer · Biomarker

Introduction

Today, in western countries, only 30 to 40 % of all invasive breast cancers are node positive [1]. The marked stage shift, which has occurred following introduction of screening mammography maintain that a defined group of patients now exists with such a low probability of nodal disease, that even sentinel lymph node biopsy can be eliminated [2]. But the group, in which axillary dissection could be omitted without any negative impact on the management outcome that would have been otherwise achieved by axillary dissection, is yet to be accurately defined.

Objective

a) To evaluate the correlation of various clinicopathological variables with axillary nodal involvement in T1 breast carcinoma. b) To identify, on the basis of observed variables, a subgroup of T1 breast carcinoma patients with low risk of axillary nodal metastases.

Materials & Methods

The study was conducted in Bombay Hospital & Medical Research Centre. From March 2012 to May 2014, the data was prospectively compiled while patients who were operated upon since January 2009 & were on regular follow up were also included in the study. A total of 100 patients were studied in the study. Clinical parameters that were recorded included age in years, tumor palpability and family history of breast

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cancer. The histopathological (HPE) data recorded included histopathological tumor size in mm, histopathological type of the tumor, Lympho-vascular invasion (LVI), histological grade of the tumor and the presence or absence of axillary nodal metastasis. The immunohistochemistry (IHC) data recorded included positivity or negativity of the tumor for oestrogen receptor (ER), progesterone receptor (PR) and epidermal growth factor receptor (Her2/*neu*). Patient inclusion Criteria included, patients with T1 breast cancer, no palpable axillary nodes & a minimum of 10 axillary nodes were dissected. Also, patients in whom axillary staging was done by using Sentinel lymph node biopsy (SLNB) were not included in the study.

The tumor size was determined using the largest dimension of the invasive tumor component as measured in the gross pathological specimen and this was categorized using TNM staging system of AJCC (7th edition): T1mic = 1 mm or less, T1a = 1.1 mm–5 mm, T1b = 5.1 to 10 mm, T1c = 11 mm to 20 mm [3].

Nottingham scheme, also called as Elliston and Ellis modification of the Scarff-Bloom Richardson grading system, was used for grading the tumors [4].

Immunohistochemical (IHC) analysis was performed on the formalin fixed, paraffin-embedded breast cancer tissue specimens. The oestrogen receptor (ER) and progesterone receptor (PR) analyses were based on the IHC assay, in which a report of 1 % or greater of the cells that had nuclear staining for either ER or PR was defined as positive [5]. IHC was performed with anti-ER (Thermo, Clone: SP1, dilution: 1:100, Fremont, CA) and anti-PR (Thermo, Clone: SP2, dilution 1:100, Fremont, CA) and using an auto staining system. The breast cancer tumors were classified as HER2-positive if they were scored as 3+ by IHC method. The intensity of the membrane staining was defined by a semi-quantitative score (0 to 3+). The tumor staining was compared to the staining of the normal breast epithelium for the same patient for the negative control. For clinical purposes, 3+ staining, which was defined as uniform and intense membrane staining in more than 30 % of the invasive breast cancer cells, was considered as overexpression [6]. Specimens which were equivocal on IHC for Her2 status were further analysed by florescent in situ hybridization (FISH) as recommended by American Society of Clinical Oncology/College of American Pathologists guidelines 2007. Such equivocal samples were defined as exhibiting complete membrane staining that is either non-uniform or weak in intensity but with obvious circumferential distribution in at least 10 % of invasive cells (corresponding to a score of 2+) [6]. The path Vysion Her2/*neu* probe kit (Vysis Inc, Downers Grove, IL) was used for the FISH analyses of such specimens. The specimens were interpreted as amplified when ratio of Her2/chromosome 17 signals was equal or greater than 2.0. We defined node positive (+) as one or more histologically documented axillary lymph nodes.

Table 1 Univariate analysis of factors associated axillary lymph node metastases

Factor	Unadjusted odds ratio and 95 % CI ^a	p-value
Tumor size (mm)		
≤5 mm tumor	1 (referent)	
5.1–10 mm tumor	1.46 (1.12~1.99)	0.06
10.1–20 mm tumor	6.48 (5.35~18.49)	<0.001
Lympho-vascular invasion		
Negative	1 (referent)	
Positive	5.41 (5.03~11.18)	<.001
Nuclear grade		
Grade I	1 (referent)	
Grade II & III	4.02 (1.89~5.11)	0.000
ER/PR/Her2 profile		
ER/PR+,Her2-	1 (referent)	
ER/PR+,Her2+	0.06 (0.01~0.29)	0.051
ER/PR-,Her2+	1.05 (0.08~2.39)	0.06
ER/PR-,Her2-	3.25 (2.02~4.39)	0.003
Palpable mass		
Negative	1 (referent)	
Positive	2.86 (2.15~3.94)	0.000
Family History		
Negative	1 (referent)	
Positive	0.58 (0.15~2.35)	0.107

^a confidence interval

Table 2 Multivariate analysis of the factors found significant on univariate analysis

Factor	Adjusted odds ratio and 95 % CI ^a	p-value
Tumor size (mm)		
≤5 mm tumor	1 (referent)	
6–10 mm tumor	1.24 (1.05~2.11)	0.05
10–20 mm tumor	4.8 (3.84~12.56)	<0.001
Lymph vascular invasion		
Negative	1 (referent)	
Positive	3.52 (2.9~9.3)	0.000
Nuclear grade		
Grade I	1 (referent)	
Grade II & III	3.5 (0.12~4.75)	0.003
ER/PR/Her2 profile		
ER/PR+,Her2-	1 (referent)	
ER/PR+,Her2+	0.02 (0.012~0.42)	0.048
ER/PR-,Her2+	0.89 (0.01~3.97)	0.01
ER/PR-,Her2-	2.14 (1.98~4.54)	0.003
Palpable mass		
Negative	1 (referent)	
Positive	1.08 (0.95~4.15)	0.04

^a confidence interval

Table 3 Biomarker panel of tumors without axillary lymph node metastases

Factor	Number	Positive ALNI	Negative ALNI
a. T1a-b (≤ 10 mm)			
b. LVI absent	12	0	12 (100.0%)
c. Grade I			

ALNI: Axillary lymph node involvement, LVI: lympho-vascular invasion

Results

Of the total 100 patients in our study, 25 (25 %) had node positive disease. The univariate analysis of the factors associated with axillary lymph node metastases is presented in Table 1. The multivariate analysis of factors associated with axillary lymph node metastases is presented in Table 2. All the variables which were found significant on univariate analysis were also found to be independent predictors of axillary lymph node metastases on multivariate analysis. Table 3 presents the biomarker profile of tumors without axillary metastases.

Discussion

Historically, the clinical value of axillary dissection in the management of breast cancer kept on changing. Evidence discredited its therapeutic value in improving the survival but proved its predictive & prognostic value and its value in the local control of breast cancer. The knowledge of ALNI influences the consideration of adjuvant chemotherapy in limited number of breast cancer patients in contemporary clinical practice. With this progressively squeezing role of axillary dissection in day to day practice, clinicians have sought to look into:

- The proportion of patients of breast cancer who are over treated for their axillae
- Alternative means of garnering the information of ALNI

Apart from observation with selective delayed treatment, the second strategy that is being evaluated is to try to predict ALNI in a tumor on the basis of biomarker profile so that management strategy for the clinically negative axillae can be individualized. Based on the predicted risk of ALNI, the axilla with low risk can be observed while axillae with

Table 4 Summary of various studies published on evaluation of predictive factors of ALNI

Author/year	Variables found predictive of ALNI on multivariate analysis					
	T size >1 cm	LVI	GII/III	T palpability	ER/PR-,Her2-	Others
Youshihara E et al. 2013 [7]	+	+	-	NE	- ¹	MF+, location +
Bezić J et al. 2011 [8]	- [†]	+	NE	NE	- ²	HT -, ploidy/S phase fraction -
Gwak G et al. 2010 [9]	-	+	+	NE	+ ⁵	Age-, MC-,ki-67-,bcl2-
Jong HL et al. 2010 [10]	+	+	NE	+	+	None
Yip CH et al. 2009 [11]	+	+	-	NE	NE	Age -, Race -
Cetintas SK et al. 2006 [12]	+	+ ^{LI}	NE	NE	NE	Age<40 +,FH +, PNI +
Tatjana IK et al. 2006 [13]	+	NE	-	-	- ³	High Ki-index +
Viale et al. 2005 [14]	+	+ ^{VI}	+ ^a	NE	+ ^{4*}	MF +, Ki ≥ 16 % -, favourable HT*
Tan et al. 2005 [15]	-	+	-	NE	+ ⁵	Age -, KI-index>10 -, bcl2 ≥ 33 % -
Badar et al. 2002 [16]	+	+	+ ^b	NE	NE	KI index ≥ 18 % +
Orucevic A et al. 2002 [17]	NE	NE	NE	NE	- ⁶	MIB index>10 +
Bevilacqua et al. 2002 [18]	+	+	+	NE	- ¹	MC +, Location +
Brenin et al. 2001 [19]	+	+ ^{LI}	+	-	- ⁷	Age -, s-phase -, ploidy -
Silverstein et al. 2001 [20]	+	+	+	+	- ¹	Age<50 -, S-phase ≥ 6.0 ,
Chua et al. 2001 [21]	+	+	-	-	NE	MF +, MC +
Rivadeneira DE et al. 2000 [22]	NA [†]	-	+	NE	- ⁶	Younger age +
Shoup M et al. 1999 [23]	+	+	+ ^b	NE	NE	None
Our study	+	+	+	+	+	None

T Tumor, LVI lymphovascular invasion, G nuclear grade, ER estrogen receptor, PR progesterone receptor, Her2 Human epidermal growth receptor, NE not evaluated, + positive, - negative, MF multifocal, MC multicentric, HT histological type, RA retroareolar, L lateral, FH family history, PNI perineural invasion, Favourable HT includes lobular, mucinous, papillary, * inverse relation, bcl2 B cell lymphoma 2, a only grade II predictive, b only Grade III predictive, [†] only tumors less than 1 cm were analysed, LI only lymphatic invasion evaluated, VI only vascular invasion evaluated, 1 receptor status of each receptor analyzed individually (ungrouped fashion), 2 evaluated for Her2 only, 3 evaluated for progesterone receptor only, 4 only PR negative status is predictive, 5 receptor status of each receptor analyzed individually (ungrouped fashion) & only Her2 over expression found predictive of ALNI, 6 only ER/PR evaluated, 7 only ER evaluated

Table 5 Biomarker tumor profiles with corresponding risk of ALNI as published by various authors

Study & Year	Predictive factors defining the group of patients with least incidence of ALNI	ALNI
Bezić J et al. 2011 [8]	≤10 mm tumors, No LVI, without Her2/neu amplification but with low S-phase fraction & diploidy	<5 %
Badar AA et al. 2002 [16]	GI/GII tumors, T≤1 cm, without LVI, Ki-67 index <18 %	4.3 %
Chua B et al. 2001 [26]	T≤5 mm, non multicentric or multifocal, without LVI or tubular or mucinous histology	0 %
Rivadeneira et al. 2000 [22]	T≤5 mm, GI, without LVI, age>60 years	8.4 %
Barth A et al. 1997 [27]	Non-palpable, non-high grade T≤1 cm, without LVI	3 %
Chadha et al. 1994 [28]	T≤1 cm without LVI	9 %
Our study	T≤1 cm, GI grade, without LVI, non-palpable	0 %

ALNI Axillary lymph-node involvement, T tumor, G nuclear grade, LVI lympho-vascular invasion

moderate-high risk could be subjected either to sentinel lymph node biopsy (SLNB) or axillary dissection. Such an approach is quiet feasible considering the fact that pre-operative core biopsies allow extensive characterization of the tumor using histopathology, immunohistochemistry, cytogenetics and fluorescent in-situ hybridization techniques (FISH). Markers which have been evaluated as independent predictors of ALNI include tumor size, lympho-vascular invasion, histological grade, clinical palpability of the tumor, ER/PR status, Her2/neu amplification, Ki-67 index, MIB-index, diploidy/polyploidy etc. Table 4 presents the published data on such evaluation of independent predictors of ALNI.

The factors, as evident from Table 4, most consistently found directly associated with ALNI include the larger tumor size and the presence of the lympho vascular invasion followed by higher histological tumor grades. The results of our study reproduced the similar findings. Tumor size of ≥1 cm (OR=4.8, 95 % CI: 3.84–12.56, $p<0.001$), grade II/III (OR=3.5, 95 % CI: 0.12–4.75, $p<0.003$) and the presence of lympho vascular invasion (OR 3.52, 95 % CI: 2.9–9.3, $p<$

0.000) are found to be the independent predictors of ALNI in our study. In our study none of the 24 patients with ≤10 mm tumors without LVI had ALNI while the ALNI was found in all the three patients with ≤10 mm tumors with LVI ($p<0.05$). In our study the significant increase in ALNI associated with LVI extended to the tumors of 10.1–20 mm size also. Against the 5.4 % of ALNI in T1c tumors without LVI, ALNI was observed in 55.6 % T1c tumors with LVI. In concordance with the reports from many authors, we observed that for a particular tumor size higher histological grades are associated with higher incidence of ALNI [9, 12, 18, 20].

In our study grade II/III T1a-b tumors had 20.% incidence of ALNI against 0 % for grade I T1a-b tumors & similarly grade II/III T1c tumors had 34.7 % incidence of ALNI against 20.8 % for grade I T1c tumors.

Tumor palpability as a factor predictive of ALNI has been studied less often and published with mixed results. Jong HL et al. [10] documented tumor palpability as an independent predictive factor of ALNI, an observation against the published results of Tatjana et al. 2006 [13]. However our study,

Table 6 Tumor biomarker profiles as suggested by various authors for consideration of omission of axillary dissection

Author & year	Proposed criteria for omission of axillary dissection	Risk of ALNI
Chua B et al. [26]	Clinically node-negative patients with either a≤5 mm & LVI – tumor, or a≤15 mm tubular or mucinous carcinoma.	NS
Fein DA et al. [29]	Tumors mammographically detected and 5 mm size	<10 %
	Mammographically detected, pathologic size 6–10 mm, age >40	
	Tubular carcinoma≤10 mm size	
Silverstein et al. [20]	pT1a tumors	<3 %
Chadha et al. [28]	Women>60 years with early stage tumor	NS
Le Bouëdec et al. [30]	pT1a tumors detected by screening mammography	NS
Maibenco et al. [31]	pT1a & pTb mucinous or tubular tumors	<5 %
	pT1a papillary or grade I tumors	
Saiz et al. [32]	pT1a tumors	NS
Halverson et al. [33]	pT1a or pT1b. pT1b if knowledge of ALNI does not change adjuvant treatment	NS
Ollivoto et al. [21]	pT1a tumors without lymphatic or vascular invasion	<5 %
Our study	≤10 mm, No LVI, Grade I	0 %

ALNI Axillary lymph node involvement, LVI -ve lympho-vascular invasion negative, NS Not specified

like Jong HL et al. [10] observations documented it to be an independent predictor of ALNI on multivariate analysis (OR = 1.08, 95 % CI: 0.95–4.15, $p < 0.04$).

ER/PR and Her2/neu status as a predictive factor of ALNI has been the most variably/heterogeneously evaluated and analysed in the literature. Some studies evaluated only ER/PR while some evaluated Her2/neu only. Even studies which have evaluated all the three receptors differ in individual versus group analysis of the factors. We believe that the heterogeneity and subsequent inconclusiveness of the resultant data might have crept in due to two main reasons: a) lack of standardization of the technique for evaluation of receptor status among the studies and b) change of definitions from time to time for their positivity and negativity. Considerable heterogeneity in breast cancer receptor evaluation as factor predictive of ALNI can be easily made from Table 4. We consider that receptor variables as factors for predicting ALNI should be analysed in grouped manner so as to collaborate with the newer approaches to the breast carcinoma classifications based on IHC biomarkers and gene expression profiling. The Basal-like type which are commonly ER/PR-, Her- (Triple negative) have been documented to have worst overall and disease free survival [24, 25].

As published by Jong HL et al. [10] our study also documented triple negative (ER/PR-, Her2-) receptor expression status to be an independent predictor of ALNI (OR = 2.14, 95 % CI: 1.98–4.54, $p < 0.003$). However Youshihara et al. [7] did not find these receptor factors as independent predictive factors in their recently published study but the study lacks analysis of these factors in a grouped manner.

Published literature (Table 4) presents mixed results for the factors such as presence of family history, histological type of the tumor as predictors of ALNI. Our study did not demonstrate any statistically significant association between these factors and the ALNI. However, a small sample size of our study prevented us from making any conclusive inference for the factors which are relatively rare in occurrence (family history & special histological types). Though many studies have found younger age as a significant predictor of ALNI, our study did not reveal any association of age with the ALNI.

Table 5 presents biomarker tumor profile with corresponding risk of ALNI as published by various authors while Table 6 depicts predictive factor criteria, as published by corresponding authors, for possible omission of axillary dissection owing to the low predictive risk of ALNI in such patients.

In our study ALNI was not observed in any of the 12 patients with a tumor size of ≤ 10 mm, no LVI & histological grade I, implying that the biomarkers predictive of ALNI have a potential to delineate a group of patients in whom operative axillary evaluation (SLNB/AD) can be substituted by a watchful follow up.

From the above discussion, it seems that scientific rationality, based on pre-operative core tissue evaluation, does exist

for identifying a group of early breast cancer patients with reasonably low risk of predicted ALNI for consideration of omission of both AD/SLNB. The standardization of definitions for the variables predictive of ALNI & quality techniques for evaluation of such biomarkers in tumor biopsy cores will be of paramount importance towards that effort. Such strategy of selective omission of AD/SLNB will require to be studied in prospective, adequately powered studies/randomized trials with sufficiently long follow up for survival outcomes. However, due to relative rarity of T1 breast cancers, it seems difficult to conduct a sufficiently powered prospective study on the subject particularly in countries where breast cancer screening is not widely prevalent.

References

1. Jtoi I (1999) Management of axilla in primary breast cancer. *Surg Clin N Am* 79:1061–1073
2. Cady B, Stone MD, Schuler J et al (1996) The new era in breast cancer: invasion, size and nodal involvement dramatically decreasing as a result of mammographic screening. *Arch Surg* 131:301–308
3. Stephen BE, Carolyn CC (2010) American joint committee on cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 17:1471–1474
4. Elston CW, Ellis IO (1991) Pathological prognostic factors in breast cancer I. The value of histological grade in breast cancer: experience from a large study with a long term follow-up. *Histopathology* 19:403–410
5. Hammond ME, Hayes DF, Dowsett M et al (2010) American society of clinical oncology/college of American pathologists guideline recommendations for immune histochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol* 28: 2784–2795
6. Wolff AC, Hammond ME, Schwartz JN et al (2007) American society of clinical oncology/college of American pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol* 25:118–145
7. Youshihara E, Smeets A, Laenen A, Reynders A, Soens J, Ongeval CV et al (2013) Predictors of axillary lymph node metastases in early breast cancer and their applicability in clinical practice. *Breast* 22(3):357–361
8. Bezić J, Samaja-Projić I, Projić P, Ljubković J, Capkun V, Tomić S (2011) Can we identify the group of small invasive (T1a,b) breast cancers with minimal risk of axillary lymph node involvement? A pathohistological and DNA flow cytometric study. *Pathol Res Pract* 207(7):438–442
9. Gwak G, Park K, Shin E, Han S, Kim JY, Kim H et al (2010) Lympho-vascular invasion and Her2/neu amplification as predictive factors for axillary lymph node metastasis in early breast cancer patients. *J Breast Cancer* 13(3):250–256
10. Jong HL, Sung HK, Young JS, Byoung YS, Hoon KK (2010) Predictors of axillary lymph node metastases in a Korean population with T1-2 breast carcinoma: triple negative breast cancer has a high incidence of axillary lymph node metastases irrespective of the tumor size. *Cancer Res Treat* 42:30–36
11. Yip CH, Taib NA, Tan GH, Ng K, Yoong BK, Choo WY (2009) Predictors of axillary lymph node metastases in breast cancer: is there a role for minimal axillary surgery? *World J Surg* 33(1):54–57

12. Cetintas SK, Kurt M, Ozkan L, Engin K, Gokgoz S, Tasdelen I (2006) Factors influencing axillary lymph node metastases in breast cancer. *Tumori* 92(5):416–422
13. Tatjana IK, Milana P, Dejan N, Stavika KU (2006) Factors correlating with lymph node metastases in patients with T1 ductal invasive breast cancer. *Arch Oncol* 14:19–22
14. Viale G, Zurrida S, Maiorano E et al (2005) Predicting the status of axillary sentinel lymph nodes in 4351 patients with invasive breast carcinoma treated in a single institution. *Cancer* 103(3):492–500
15. Tan LG, Tan YY, Heng D, Chan MY (2005) Predictors of axillary lymph node metastases in women with early breast cancer in Singapore. *Singapore Med J* 46:693–697
16. Badar AA, Tio J, Petru E, Buhner M, Pfhalberg A, Volkholz A, Tulusan AH (2002) T1 breast cancer: identification of patients at low risk of axillary lymph node metastases. *Breast Cancer Res Treat* 76:11–17
17. Orucevic A, Reddy VB, Bloom KJ, Bitterman P, Magi-Galluzi C, Oleske DM, Phillips M, Gould VE, Cobleigh M, Wick MR, Gattuso P (2002) Predictors of lymph node metastasis in T1 breast carcinoma, stratified by patient age. *Breast J* 8:349–355
18. Bevilacqua JLB, Cody HS, Macdonald KA, Tan LK, Borgen PI, Van Zee KJ (2002) A model for predicting axillary lymph node metastases on the basis of 2000 sentinel lymph node positions and tumor position. *EJSO* 28:490–500
19. Brenin DR, Manasseh DM, El Tamer M et al (2001) Factors correlating with lymph node metastases in patients with T1 breast cancer. *Ann Surg Oncol* 8(5):432–437
20. Silverstein MJ, Gierson ED, Waisman JR, Senofsky GM, Colburn WJ, Gamagami P (1994) Axillary lymphnode dissection for T1a breast carcinoma: is it indicated. *Cancer* 73:664–667
21. Olivotto IA, Jackson JS, Mates D, Andersen S, Davidson W, Bryce CJ et al (1998) Prediction of axillary lymph node involvement of women with invasive breast carcinoma: a multivariate analysis. *Cancer* 83:948–955
22. Rivadeneira DE, Simmons RM, Christos PJ, Hanna K, Daly JM, Osborn MP (2000) Predictive factors associated with axillary lymph node metastases in T1a and T1b breast carcinomas: analysis in more than 900 patients. *J Am Coll Surg* 191(1):1–8
23. Shoup M, Malinzak M, Weisenberger J, Aranhava JV (1999) Predictors of axillary lymph node metastasis in T1 breast carcinoma. *Am Surg* 65:748–753
24. Perou CM, Sorlie T, Eisen MB et al (2000) Molecular portraits of human breast tumors. *Nature* 406(6797):747–752
25. Sorlie T, Perou CM, Tibshirani R et al (2001) Gene expression patterns of breast carcinoma distinguish tumor subclasses with clinical implication. *Proc Natl Acad Sci USA* 98(19):10869–10874
26. Chua B, Ung O, Taylor R, Boyages J (2001) Frequency and predictors of axillary lymph node metastases in invasive breast cancer. *ANZ J Surg* 71:723–728
27. Barth A, Craig PH, Silverstein MJ (1997) Predictors of axillary lymph node metastases in patients with T1 breast carcinoma. *Cancer* 79(10):1918–1922
28. Chadha M, Chaban AB, Friedmann P, Vikram B (1994) Predictors of axillary lymph node metastases in patients with T1 breast cancer. *Cancer* 73:350–353
29. Fein DA, Fowble BL, Hanlon AL, Hooks MA, Hoffman JP, Sigurdson ER, Jardines LA, Eisenburg BL (1997) Identification of women with T1-T2 breast cancer at low risk of positive axillary nodes. *J Surg Oncol* 65:34–39
30. Le Bouëdec G, Pomel C, Chamussy E, Feillel V, De Latour M, Dauplat J (1996) Le curage ganglionnaire axillaire dans les cancers infracliniques du sein. *Bull Cancer* 83:581–588
31. Maibenco DC, Weiss LK, Pawlish KS, Severson RK (1999) Axillary lymph node metastases associated with small invasive breast carcinoma. *Cancer* 85:1530–1536
32. Saiz E, Toonkel R, Poppiti RJ, Robinson MJ (1999) Infiltrating breast carcinoma smaller than 0.5 centimeters: is lymph node dissection necessary? *Cancer* 85:2206–2211
33. Halverson KJ, Taylor ME, Perez CA, Garcia DM, Myerson R, Philpott G et al (1994) Management of the axilla in patients with breast cancers one centimeter or smaller. *Am J Clin Oncol* 17:461–466