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Development of a prediction model for lymph node metastasis in luminal A subtype breast cancer: The possibility to omit sentinel lymph node biopsy

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ABSTRACT

The present study aimed to construct a prediction model for axillary lymph node metastasis (ALNM) using a DNA microarray assay for gene expression in breast tumor tissues. Luminal A breast cancers, diagnosed by PAM50 testing, were analyzed, and a prediction model (genomic nodal index (GNI)) consisting of 292 probe sets for ALNM was constructed in a training set of patients (n = 388), and was validated in the first (n = 59) and the second (n = 103) validation sets. AUCs of ROC were 0.820, 0.717, and 0.749 in the training, first, and second validation sets, respectively. GNI was most significantly associated with ALNM, independently of the other conventional clinicopathological parameters in all cohorts. It is suggested that GNI can be used to identify the patients with a low risk for ALNM so that sentinel lymph node biopsy can be spared safely.

Introduction

Axillary lymph node dissection (ALND) has been the gold standard for breast cancer surgery for many years, but has recently been replaced with the less invasive sentinel lymph node biopsy (SLNB) for clinically node-negative breast cancer patients. Not only does SLNB have a low false-negative rate of 7.9–9.7%, but randomized clinical studies also show that the recurrence rates of distant organs and the axillary lymph node are similar between patients treated with SLNB and ALND [1,2]. Although the incidence of long-term comorbidities including sensory neuropathy, lymphedema, and motor neuropathy is significantly lower in patients treated with SLNB than ALND, the fact that a significant percentage (8.6–15%, 3–6.9%, and 3–3.8%, respectively) of patients treated with SLNB still experience them is noteworthy [3–5]. Moreover, the rate of sentinel lymph node (SLN) metastasis is reported to be 28.9–42.0% in patients with clinically node-negative cancer, indicating that more than half of these patients have no SLN metastasis [3] so do not require SLNB.

A method of predicting axillary lymph node metastasis (ALNM) preoperatively is likely to be helpful in selecting those patients for whom SLNB is needed. While tumor size, lymphovascular invasion, histological grade, etc. are reported to be associated with lymph node (LN) metastasis [6–8], they are not thought to be sufficiently accurate to identify patients unlikely to experience ALNM for whom SLNB can be safely omitted. Moreover, these parameters can only be determined postoperatively following histological examination of the tumors, indicating that they cannot be used in the preoperative evaluation of the ALNM risk.

DNA microarray assays for the evaluation of gene expression in breast cancer tissues have been used to develop several gene classifiers for the prediction of recurrence [9–11] and response to chemotherapy [12,13]. One devised by Smeets et al. is currently used as a predictor for ALNM [14], but accuracy levels do not appear to be sufficiently high, necessitating the development of a more accurate predictor.

Recent advances in DNA microarray assays for gene expression have revealed several intrinsic subtypes (luminal A, luminal B, HER2-enriched, basal-like, and normal breast-like) of breast cancers, each of which shows a distinct gene expression profile and biological characteristics exemplified by the difference in their prognosis [15], response to chemotherapy [16], and rate of LN metastases [17]. Although conventional studies on the parameters associated with ALNM have usually been carried out on all subtypes of breast cancers, the fact that the biology, including the rate of ALNM, differs between subtypes indicates that a new predictor for ALNM should be investigated for each subset. The

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Table 1
Clinicopathological characteristics of patients included in the training set, the first validation set, and the second validation set.

	Training set				First validation set				Second validation set			
	All patients	Nodal status		*P*-value	All patients	Nodal status		*P*-value	All patients	Nodal status		*P*-value
	(n = 388)	Negative (n = 192)	Positive (n = 196)		(n = 59)	Negative (n = 28)	Positive (n = 31)		(n = 103)	Negative (n = 51)	Positive (n = 52)	
Age (years)												
⩽50	66	26	40	0.063	24	10	14	0.597	29	14	15	1.000
>50	190	102	88		35	18	17		61	29	32	
Unknown	132	64	68		0	0	0		13	8	5	
Tumor diameter (mm)												
⩽20	139	96	43	1.73E−09	22	11	11	0.793	57	37	20	7.08E−04
>20	154	52	102		37	17	20		46	14	32	
Unknown	95	44	51		0	0	0		0	0	0	
Tumor stage												
T1	139	96	43	1.29E−08	22	11	11	0.949	41	27	14	0.081
T2	127	47	80		35	16	19		27	10	17	
T3	26	5	21		2	1	1		4	1	3	
T4	1	0	1		0	0	0		2	1	1	
Unknown	95	44	51		0	0	0		29	12	17	
Histological grade												
1	113	64	49	0.12	21	11	10	0.419	27	18	9	2.81E−03
2	144	69	75		33	14	19		43	24	19	
3	107	46	61		4	3	1		24	5	19	
Unknown	24	12	12		1	0	1		9	4	5	
ER												
Positive	367	176	191	0.081	59	28	31	N.A.	90	48	42	0.475
Negative	12	9	3		0	0	0		8	3	5	
Unknown	9	7	2		0	0	0		5	0	5	
PR												
Positive	245	112	133	0.147	47	21	26	0.521	49	28	21	0.688
Negative	35	21	14		12	7	5		7	3	4	
Unknown	108	59	49		0	0	0		47	20	27	
HER2												
Positive	27	11	16	0.418	8	1	7	0.055	9	2	7	0.081
Negative	229	115	114		51	27	24		74	41	33	
Unknown	132	66	66		0	0	0		20	8	12	
Ki67												
Positive	29	11	18	0.630	13	5	8	0.534	1	0	1	0.194
Negative	44	20	24		45	23	22		35	29	6	
Unknown	315	161	154		1	0	1		67	22	45	
Lymphatic invasion												
0	0	0	0	N.A.	25	10	15	0.100	11	10	1	0.951
1	0	0	0		22	14	8		11	10	1	
2	0	0	0		8	2	6		0	0	0	
3	0	0	0		2	0	2		1	1	0	
Unknown	388	192	196		2	2	0		80	30	50	
Vascular invasion												
0	0	0	0	N.A.	55	24	31	0.204	22	20	2	1.000
1	0	0	0		2	2	0		1	1	0	
2	0	0	0		0	0	0		0	0	0	
3	0	0	0		0	0	0		0	0	0	
Unknown	388	192	196		2	2	0		80	30	50	
Node stage												
N0	192	192	0	N.A.	28	28	0	N.A.	51	51	0	N.A.
N1	8	0	8		19	0	19		27	0	27	
N2	7	0	7		9	0	9		0	0	0	
N3	0	0	0		3	0	3		0	0	0	
Unknown	181	0	181		0	0	0		25	0	25	
GNI												
<0	192	148	44	5.95E−15	29	20	9	1.69E−03	41	30	11	1.19E−04
⩾0	196	44	152		30	8	22		62	21	41	

ER, estrogen receptor; GNI, genomic nodal index; HER2, human epidermal growth factor receptor; PR, progesterone receptor; N.A., not available.

luminal A subtype breast cancer has been studied in so many papers that a large amount of gene expression data is available in public databases, which are suitable for the construction of a predictive model for ALNM. Moreover, luminal A breast cancers are the least aggressive subtype biologically, so that even if false-negative cases are encountered in which ALNM is overlooked, this is less likely to be a clinically serious problem provided that incidences are low. Therefore, in the present study, we attempted to develop a prediction model for ALNM using DNA microarray and the luminal A subtype of breast cancer.