Original Article

Validation of international predictive nomograms for non-sentinel lymph node metastases in Hong Kong breast cancer patients with positive sentinel lymph nodes

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Background: Management of the axilla in breast cancer patients has been evolving over the past decade with progressive de-escalation in axillary surgery. In this study, we investigated the factors predicting non-sentinel lymph node (NSLN) metastases in sentinel lymph node (SLN) positive breast cancer patients in Hong Kong and assessed international predictive scoring systems [Memorial Sloan Kettering Cancer Center (MSKCC), MD Anderson Cancer Center (MDACC), Tenon score] for their accuracy and applicability in our locality.

Methods: This is a retrospective study of 126 breast cancer patients who received completion axillary dissection after a positive SLN biopsy (SLNB) between April 2011 and April 2019. Their MSKCC, MDACC and Tenon predictive scores for NSLN metastases were compared with receiver operating characteristic (ROC) analysis. Multivariate logistic regression was performed to identify independent predictors of non-sentinel node metastases.

Results: The majority had early disease, with only 7.1% (9 patients) having T3 disease. Only 35 patients (27.8%) had positive NSLN after axillary dissection. The area under the ROC curve (AUROC) of MDACC (0.708, 95% CI: 0.583–0.833) was the highest, followed by MSKCC (0.674, 95% CI: 0.553–0.795) and Tenon (0.660, 95% CI: 0.531–0.789). The AUROC improved after excluding patients with micrometastases only on SLNB. All three normograms showed poorer performance when there was only one positive SLN. Multivariate analysis found grade (OR: 0.107, 95% CI: 0.14–0.801, P=0.03), ratio of positive to negative SLN (OR: 0.005, 95% CI: 0.001–0.639, P=0.033) and extranodal spread (OR: 2.754, 95% CI: 0.979–7.745, P<0.05) as significant independent predictors of NSLN metastases.

Conclusions: MSKCC, MDACC and Tenon scores all show acceptable accuracy in predicting NSLN metastases but are less accurate in patients with only one positive SLN or micrometastases. MDACC shows the best accuracy in our subset of patients in Hong Kong.

Keywords: Breast cancer; sentinel lymph node (SLN); axillary lymph node dissection (ALND); nomogram

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Introduction

Breast cancer is the most common cancer in women and its incidence in Hong Kong has doubled over the past 10 years, resulting in a great health burden. One in 15 women develop breast cancer over the course of their lifetime (1). In 2016 alone, 4,132 patients were diagnosed with breast cancer and

Table 1 Validation of MSKCC, MDACC and Tenon scores in Asian regions

Authors [date of publication]	Region	Duration	Number of patients	NSLN metastases (%)	Number of patients with macrometastases in SLN (%)	Nomograms	AUROC
Kuo *et al.* [2013]	Taiwan	1999–2011	324	88 (27.2)	Not mentioned	MSKCC	0.738
Chue *et al.* [2014]	Singapore	2004–2009	266	147 (55.3)	Not mentioned	MSKCC	0.716
Wu *et al.* [2018]	China	2010–2016	236	105 (44.5)	224 (94.9)	MSKCC	0.677
						Tenon	0.673
Sasada *et al.* [2012]	Japan	2000–2009	116	53 (46.0)	Not mentioned	MSKCC	0.730
Tanaka *et al.* [2013]	Japan	2002–2010	89	31 (34.8)	59 (66.2)	MSKCC	0.701
Cho *et al.* [2008]	Korea	2004–2007	82	39 (47.6)	Not mentioned	MSKCC	0.786
						MDACC	0.691
						Tenon	0.751

MSKCC, Memorial Sloan Kettering Cancer Center; MDACC, MD Anderson Cancer Center; NSLN, non-sentinel lymph node; SLN, sentinel lymph node; AUROC, area under the receiver operating characteristic curve.

704 patients died from it, accounting for 12.2% of all cancer related deaths in women.

Axillary lymph node status is one of the most important prognostic predictors. Hence, accurate axillary staging is of paramount importance in treatment planning. Over the past decades, breast cancer treatment has been evolving with a paradigm shift towards "less is more", particularly evident in the de-escalation of axillary surgery. With the publication of the NSABP B32 trial (2), routine axillary lymph node dissection (ALND) is now out of favour and replaced by sentinel lymph node biopsy (SLNB) in clinically node negative patients for axillary staging. The ASOCOG Z0011 trial also suggests that ALND can be omitted in selected patients with positive sentinel lymph nodes (SLNs) undergoing breast conservation treatment with no detrimental effect on their 10-year overall survival and locoregional recurrence risk (3,4). Though the role of ALND has been on the decline (5,6), for patients not fulfilling the Z0011 criteria, ALND is still the standard treatment. Yet, up to 40–70% of these patients do not have further metastases in their non-SLNs (NSLNs) after axillary dissection (7,8); and they are exposed to a risk of lymphedema of up to 25–40%, arm paraesthesia up to 30%, pain and reduced shoulder movement (9,10).

Can there be a way to predict which patient would truly benefit from an axillary dissection? Several nomograms have been developed with the aim of predicting the risk of non-sentinel lymph metastasis, including the Memorial Sloan Kettering Cancer Center (MSKCC) (11), the MD Anderson Cancer Center (MDACC) nomogram (12), Tenon (13), Stanford (14), Cambridge (15), etc. Though these nomograms have been developed in Caucasian countries, multiple validation studies have been performed in predominantly Asian populations such in Korea (16), Japan (17,18), Taiwan (19), Singapore (20) and China (Mainland) (21). The results of these studies are summarized in *Table 1*.

Hong Kong breast cancer patients have an earlier age of onset compared with their western counterparts, and the highest 5-year relative survival rate amongst Asian countries (22). Hence, deciding on optimal axillary management is crucial. This study represents the first study in Hong Kong validating MSKCC, MDACC and Tenon scores on prediction of NSLN metastases, with additional subgroup analysis on patients with minimal axillary disease burden. We selected these nomograms for validation in our patients as they are easily accessible and easy to calculate, facilitating its use in the frontline for risk assessment, patient communication and individualization of treatment.

We present the following article in accordance with the TRIPOD reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-20/rc).

Methods

This is a retrospective study of patients with primary breast cancer who received surgery between April 2011 and April 2019 in Queen Elizabeth Hospital, Hong Kong, China.

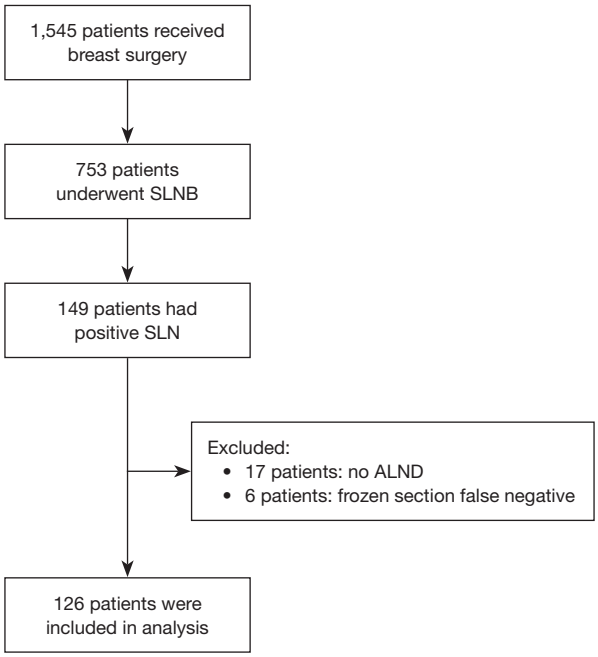


Figure 1 Flowchart of patient recruitment. SLNB, sentinel lymph node biopsy; SLN, sentinel lymph node; ALND, axillary lymph node dissection.

Patients are eligible for inclusion into this study if they fulfilled these criteria: (I) clinically node negative with no distant metastasis on diagnosis; (II) underwent ipsilateral successful SLNB with frozen section positive for metastasis (macrometastases or micrometastases); (III) received axillary dissection. Patients were excluded if they (I) were diagnosed to have solely ductal carcinoma *in situ*; (II) had axillary lymph node metastases or distant metastases on presentation; (III) received neoadjuvant chemotherapy; (IV) were recurrence of previous breast cancer.

Demographic data including age, gender, diagnostic investigations, operative details, tumour attributes [grade, lymphovascular invasion, size, hormone receptor and human epidermal growth factor receptor 2 (HER2) status], details of SLNB, axillary dissection and their results were collected.

From the collected data, predicted risk of NSLN metastases was calculated from the following websites:

(I) MSKCC predictive results were calculated from the online calculator at http://nomograms.mskcc.org/Breast/BreastAdditionalNonSLNMetastasesPage.aspx;

(II) MDACC results were analysed according to the calculator at http://www3.mdanderson.org/app/medcalc/bc_nomogram2/index.cfm?pagename=nsln.

Tenon score was calculated from combination of three parameters with reference to the system pioneered by Barranger *et al.* (13): (I) presence of macrometastases in SLNs gives a score of 2; otherwise it gives 0. (II) A histological tumour size of more than 2 cm gives a score of 3; 1.1–2 cm gives a score of 1.5; and less than or equal to 1 cm gives a score of 0. (III) If the proportion of involved sentinel nodes among all sentinel nodes is 1, then the score is 2; those between 0.5 to 1 gives a score of 1 and less than 0.5 gives 0. Patients with a combined score of 3.5 or less had a 97.3% chance of being free from NSLN metastases.

Statistical analyses

Statistical analyses were performed with SPSS version 23. The accuracy of the MSKCC nomogram, MDACC, and Tenon scores in predicting NSLN metastases was assessed by the receiver operating characteristic (ROC) curve analysis. A greater area under the ROC curve (AUROC) equals superior concordance between predicted and observed outcomes. Multivariate analysis by logistic regression was performed to determine the independent predictors of NSLN metastases in our patient population. A P value of <0.05 represented statistical significance.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This research has been approved by Hong Kong Kowloon Central cluster research ethics committee (Ref: KC/KE-19-0134/ER-3). Informed consent has been waived by the ethics committee as this retrospective research poses no risk to patients.

Results

A total of 1,545 patients received breast surgery in the study period, of which 126 patients were eligible for inclusion. A flowchart of patient recruitment is shown in *Figure 1*. Their demographics and tumour characteristics are summarized in *Table 2*.

The majority of patients had early-stage disease, only 7.1% (9 patients) had T3 disease. SLNs were predominantly localized with isotope (65.1%) and supplemented with blue dye (15.9%) if localization was deemed poor on lymphoscintigraphy. The majority of positive SLNs were macrometastases (76.2%). Only 35 patients out of 126 (27.8%) had subsequent positive

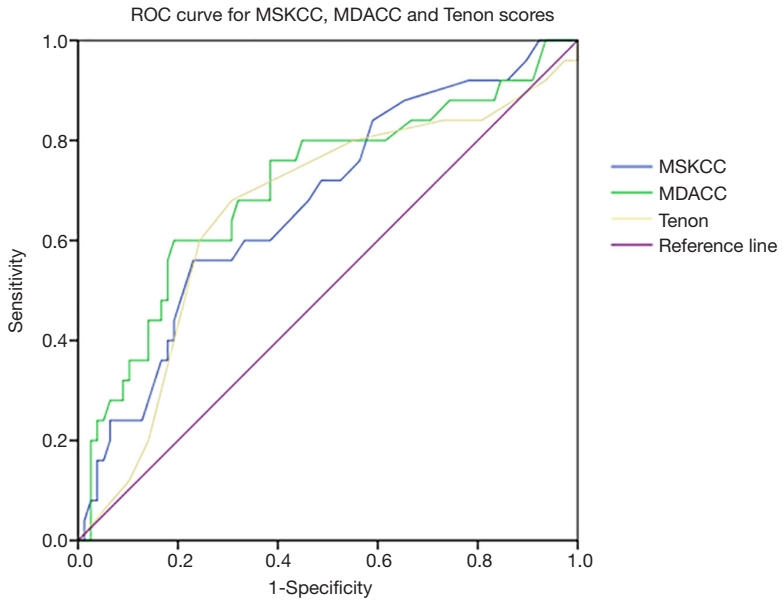
Table 2 Patient demographics

Characteristics	Number of patients (%)
Age (mean)	56.73
Gender (female)	126 (100.0)
Type of operation	
Mastectomy	88 (69.8)
BCT	38 (30.2)
T stage	
T1	52 (41.3)
T2	65 (51.6)
T3	9 (7.1)
T4	0 (0.0)
Grade (modified Bloom and Richardson)	
1	26 (20.6)
2	59 (46.9)
3	41 (32.5)
Lymphovascular invasion	
Present	68 (55.3)
Absent	55 (44.7)
Multifocal	
Yes	25 (19.8)
No	101 (80.2)
Type of tumour	
Invasive ductal	113 (89.7)
Invasive lobular	3 (2.4)
Others	10 (7.9)
ER status	
Positive	100 (79.4)
Negative	26 (20.6)
PR status	
Positive	90 (71.4)
Negative	36 (28.6)
HER2 status	
Positive	20 (16.3)
Negative	102 (82.9)
Equivocal	1 (0.8)
Method of SLN localization	
Dye	24 (19.0)
Isotope	82 (65.1)
Both	20 (15.9)
Number of SLN (median)	4 (range, 1–13)
Number of positive SLN (median)	1 (range, 1–4)
Type of positive SLN	
Macrometastases	96 (76.2)
Micrometastases	30 (23.8)
Positive NSLN present	35 (27.8)
Number of positive NSLN (median)	1 (range, 1–9)
N stage	
1mi	23 (18.3)
1	87 (69.0)
2	15 (11.9)
3	1 (0.8)
Extranodal spread	
Present	37 (31.1)
Absent	82 (68.9)

BCT, breast conserving treatment; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; SLN, sentinel lymph node; NSLN, non-sentinel lymph node.

NSLNs after axillary dissection, and amongst these patients, the majority had only 1–2 further positive NSLNs.

From this demographic data, ROC analysis was performed and the AUROC of MSKCC, MDACC and Tenon scores are shown in *Figure 2*. The AUROC of MDACC (0.708, 95% CI: 0.583–0.833) was the highest, followed by MSKCC (0.674, 95% CI: 0.553–0.795) and Tenon (0.660, 95% CI: 0.531–0.789). Further subgroup analysis performed after exclusion of patients with only micrometastases in their SLNs showed major improvement in the AUROC of MDACC (0.745, 95% CI: 0.635–0.855, P<0.005) and MSKCC (0.701, 95% CI: 0.584–0.819, P=0.003). The AUROC of Tenon score remained similar (0.656, 95% CI: 0.540–0.773, P=0.021). Subgroup analysis



Area under the ROC curve (AUROC)		
	Area	95% confidence interval
MSKCC	0.674	0.553–0.795 (P=0.009)
MDACC	0.708	0.583–0.833 (P=0.002)
Tenon	0.660	0.531–0.789 (P=0.016)

Figure 2 ROC curve for MSKCC, MDACC and Tenon scores. ROC, receiver operating characteristic; MSKCC, Memorial Sloan Kettering Cancer Center; MDACC, MD Anderson Cancer Center.

of patients with only one positive SLN found that all three nomograms showed poor performance for predicting NSLN metastases. The AUROC of MDACC (0.618, 95% CI: 0.457–0.779, P=0.21) was still the highest, compared with MSKCC (0.597, 95% CI: 0.453–0.741, P=0.21) and Tenon score (0.529, 95% CI: 0.368–0.690, P=0.71).

Multivariate analysis performed found grade (OR: 0.107, 95% CI: 0.14–0.801, P=0.03), ratio of positive to negative SLN (OR: 0.005, 95% CI: 0.001–0.639, P=0.033) and extranodal spread (OR: 2.754, 95% CI: 0.979–7.745, P<0.05) as significant independent predictors of NSLN metastases.

Discussion

Accurate assessment of nodal status is paramount in staging and treatment of early breast cancer. Since the introduction of SLNB for breast cancer in 1990s (23), deciding which patients warrant completion axillary dissection has become a conundrum of modern breast surgery. Particularly when the majority of NSLNs are negative, meaning patients are exposed to increased risks of permanent morbidity with no additional benefit.

How do we balance the risk of understaging against overtreating the axilla? In the era of Z0011, axillary dissection is no longer the only standard of care and can be safely omitted in a select group of patients receiving breast conserving surgery. However, there are still lingering concerns with the ASCOG Z0011 trial. Over half of the patients without axillary dissection received "high tangent" radiotherapy which covered the axilla (24). This complicates interpretation of results and raises the possibility that the excellent oncological outcomes may be contributed by incidental axillary irradiation. Subsequent trials designed to address the limitations of Z0011 and to expand its inclusion criteria are currently underway. For example, the UK POSNOC (POsitive Sentinel NOde: adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy) trial (25) and the Holland BOOG 2013-07 trial (26). Both trials have expanded the Z0011 criteria to encompass mastectomy patients randomized to receive either axillary treatment (ALND or radiotherapy) or no

treatment.

While we wait for results of these ongoing trials, researchers investigated predictors of NSLN metastases (27-29) hoping to find that magic cut-off to stratify patients to high risk versus low risk of further lymph node metastases. One such study by Hung *et al.* in Hong Kong (30) identified tumour size less than 3 cm, a single metastatic SLN, micrometastases and absence of extranodal spread as negative predictors for NSLN metastases. Similar results were obtained from our multivariate analysis. We identified grade, positive to negative SLN ratio and presence of extranodal spread as independent predictors of non-sentinel node metastases. Indeed, these parameters are common among formulas developed to predict the risk of NSLN metastases. There are more than 10 similar predictive nomograms developed all over the world, with MDACC, MSKCC and Tenon scores being three of the more heavily researched and validated ones (31).

From our results, all three nomograms show acceptable accuracy in predicting NSLN metastases. Among them, the MDACC calculator is the most accurate with an AUROC of 0.708. This is in line with the results of previous validation studies, which showed an AUROC ranging from 0.58 to 0.79 for MSKCC and 0.706–0.73 (32,33) for MDACC. Some studies have suggested that these nomograms are less accurate for patients with only micrometastases in their sentinel nodes (34,35). Our results indeed concur. Subgroup analysis of patients with only one positive SLN also showed poor predictive accuracy in all three nomograms. This suggests that in patients with minimal axillary disease burden, none of these predictive algorithms are perfect, and certainly not enough to justify omitting axillary dissection just based on their scores.

There are also other limitations of these algorithms. In particular, the MSKCC is only limited for invasive ductal carcinoma and invasive lobular carcinoma and cannot be used on patients with other types of breast cancer like mucinous or papillary carcinoma. In addition, most of the parameters used for calculation such as presence of lymphovascular invasion, exact tumour size, etc. are only available in the post-operative stage. This limits their use in pre-operative counselling and guiding intraoperative decisions.

Yet, despite these limitations, we believe that these nomograms still have a role in clinical practice. This study has validated the use of MDACC, MSKCC and Tenon score in patients in Hong Kong. In our institution, they are currently used to estimate the probability of NSLN metastases in patients who have had false negative SLNs to facilitate counselling on the pros and cons of further axillary treatment. They are also incorporated into oncology protocols to assist decision making during adjuvant radiotherapy planning—regional RT is omitted in a subset of breast cancer patients who did not receive completion ALND with an estimated low risk of further NSLN metastases.

This validation study represents the first of such study conducted in Hong Kong. However, it is limited by the small sample size. Despite including patients over 8 years, only a small proportion of them had positive NSLNs. There is also a selection bias and further limitation in the sample size, as this study spanned across a paradigm shift after the publication of the Z0011 study, resulting in omission of axillary dissection in a number of patients who would have been considered eligible in the initial years of this study but now rendered ineligible for inclusion. There was also some missing data regarding the presence of extranodal spread (total seven patients) before pathology reporting was standardized. Since this information is required for the calculation of MDACC scores, these patients were excluded in the analysis.

Conclusions

In conclusion, MSKCC, MDACC and Tenon scores all show acceptable accuracy in predicting NSLN metastases, but are less accurate in patients with only one positive SLN or micrometastases. MDACC shows the best accuracy in predicting NSLN metastases in our subset of patients in Hong Kong.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://abs.amegroups.com/article/view/10.21037/abs-21-20/rc

Data Sharing Statement: Available at https://abs.amegroups.com/article/view/10.21037/abs-21-20/dss

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://abs.amegroups.com/article/view/10.21037/abs-21-20/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This research has been approved by Hong Kong Kowloon Central cluster research ethics committee (Ref: KC/KE-19-0134/ER-3). Informed consent has been waived by the ethics committee as this retrospective research poses no risk to patients.

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