Original ariticle

Validation of Memorial Sloan-Kettering Cancer Center Nomogram to predict the risk of non-sentinel lymph node metastasis in sentinel node positive in Thai breast cancer patients

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Background: *Complete axillary node dissection (ALND) remains the standard of care for breast cancer with sentinel lymph node (SLN) metastasis. However, 40-70% of patients have no axillary nodes other than the SLN itself, signifying the non-necessity of ALND. To date, Memorial Sloan-Kettering Cancer center (MSKCC) has developed a nomogram to predict the risk of non-SLN metastasis. Several validation studies show the accuracy of this nomogram in Western population, but few in Asia and never in Thailand.* ***Objective:*** *The aims of this study were to validate MSKCC nomogram to predict the risk of non-SLN metastasis after SLN positive, and to evaluate the relationship between variability of clinicopathologic factors and non-SLN metastasis.* ***Methods:*** *The MSKCC nomogram was used for calculating the probability of non-SLN metastasis in 92 breast cancer patients at Pramongkutklao Hospital. Multivariate analyses were performed to evaluate the relationship between non-SLN metastases and variable factors. The predictive accuracy was compared with the MSKCC model. A receivers operating characteristics (ROC) curve was plotted, and the area under the curve (AUC) was calculated to access the discriminative power.* ***Results:*** *Additional non-SLN metastases were identified in 52/92 (56%) patients. The presence of LVI, multifocality, and Her-2 positive 3+ were identified as independent predictors for non-SLN status in multivariate analysis. The MSKCC nomogram showed an area under the ROC curve (AUC) value of 0.78 (95%CI: 0.688-0.877) after the validation for our collectives.* ***Conclusions:*** *This MSKCC nomogram revealed good validation to predict the risk of non-sentinel lymph node metastasis in sentinel node positive in Thai breast cancer patients.*

Keywords: ● *Breast cancer* ● *Sentinel lymph node biopsy* ● *Axillary lymph node dissection* ● *Metastasis* ● *Nomogram* ● *Validation*

RTA Med J 2021;74(4):261-8.

Received 5 February 2021 Corrected 25 July 2021 Accepted 21 August 2021

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นิพนธ์ต้นฉบับ

ความน่าเชื่อถือของตัวชี้วัดของสถาบันมะเร็งเมมโมเรียลสโลนแคทเทอร์ริ่ง ในการพยากรณ์การกระจายของมะเร็งมาที่ต่อมน้ำเหลืองต่อมอื่นของรักแร้ ในผู้ป่วยมะเร็งเต้านมชาวไทย

วิจิตรา อาสาฟ์ห์ประกิต สุดารัตน์ ชัยเพียรเจริญกิจ วิชัย วาสนสิริ สุรพงษ์ สุภาภรณ์ และ สุขไชย สารทถาพร
กองศัลยกรรม โรงพยาบาลพระมงกุฎเกล้า

บทคัดย่อ

บทนำ *การผ่าตัดเลาะต่อมน้ำเหลืองบริเวณรักแร้ออกทั้งหมดยังคงเป็นวิธีมาตรฐานในการรักษาผู้ป่วยมะเร็งเต้านมที่มีการกระจายมาที่ต่อมน้ำเหลืองต่อมแรกของรักแร้ อย่างไรก็ตามร้อยละ 40-70 ของผู้ป่วยพบว่าไม่มีการกระจายของมะเร็งมาที่ต่อมน้ำเหลืองต่อมอื่นของรักแร้ ทำให้การผ่าตัดเลาะต่อมน้ำเหลืองบริเวณรักแร้ออกทั้งหมดจึงไม่จำเป็น ปัจจุบันพบว่าสถาบันมะเร็งเมมโมเรียลสโลนแคทเทอร์ริ่งได้พัฒนาตัวชี้วัดในการพยากรณ์การกระจายของมะเร็งมาที่ต่อมน้ำเหลือง อย่างไรก็ตามความแม่นยำของตัวชี้วัดนี้มีรายงานส่วนใหญ่ในผู้ป่วยทางประเทศตะวันตกเท่านั้น* ***วัตถุประสงค์*** *เพื่อศึกษาความแน่นยำของตัวชี้วัดในการพยากรณ์การกระจายของมะเร็งมาที่ต่อมน้ำเหลืองของสถาบันมะเร็งเมมโมเรียลสโลนแคทเทอร์ริ่งและศึกษาความสัมพันธ์ลักษณะทางพยาธิวิทยาและการกระจายของมะเร็งมาที่ต่อมน้ำเหลืองต่อมอื่นของรักแร้* ***วิธีการศึกษา*** *เป็นการเก็บข้อมูลในผู้ป่วยที่ได้รับการผ่าตัดเลาะต่อมน้ำเหลืองบริเวณรักแร้ออกทั้งหมดที่เข้ารับการรักษาที่โรงพยาบาลพระมงกุฎเกล้า นำผลที่ได้มาวิเคราะห์แบบหลายตัวแปร* ***ผลการวิจัย*** *ผู้ป่วย 92 รายที่มีการกระจายมาที่ต่อมน้ำเหลืองต่อมแรกของรักแร้ มี 52 รายที่มีการกระจายมาที่ต่อมน้ำเหลืองต่อมอื่นของรักแร้ (ร้อยละ 56) การมีการลุกลามของมะเร็งไปที่ทางเดินน้ำเหลืองหรือหลอดเลือด การพบมะเร็งแบบหลายจุด การมีตัวรับแบบเฮอร์ทูมากกว่า 3 บวก เป็นปัจจัยที่พบว่าจะมีการกระจายของมะเร็งมาที่ต่อมน้ำเหลืองต่อมอื่นของรักแร้ ตัวชี้วัดของสถาบันมะเร็งเมมโมเรียลสโลนแคทเทอร์ริ่งแสดงความน่าเชื่อถือได้ดี* ***สรุป*** *การใช้ตัวชี้วัดของสถาบันมะเร็งเมมโมเรียลสโลนแคทเทอร์ริ่งแสดงความน่าเชื่อถือได้ดีในการพยากรณ์การกระจายของมะเร็งมาที่ต่อมน้ำเหลืองต่อมอื่นของรักแร้ในผู้ป่วยมะเร็งเต้านมชาวไทย*

คำสำคัญ: ● *มะเร็งเต้านม* ● *มะเร็งต่อมน้ำเหลือง* ● *การผ่าตัดเลาะต่อมน้ำเหลือง* ● *การแพร่กระจาย* ● *โนโมแกรม* ● *ตรวจสอบ*

เวชสารแพทย์ทหารบก 2564;74(4):261-8.

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Introduction

Axillary node status is an essential and important prognostic factor for breast cancer patients. Nowadays, sentinel lymph node (SLN) biopsy has replaced the conventional axillary node dissection (ALND). Also, it is a worldwide standard for accurate staging procedure in early-stage breast cancer, with lower morbidity from lymphedema, sensory disturbance, and shoulder dysfunction in SLN biopsy than axillary node dissection (ALND).[1-3] For 1-2 nodes of SLN macro-metastasis, the benefit of ALND on survival is currently debated.[1,2] However, 40% to 70% of positive SLN metastasis shows no additional non-SLN node involvement.[4-6] Thus, ALND is unnecessary in SLN metastasis patients. Meanwhile, nomograms and scoring systems have been suggested in several studies to predict patients whom ALND should be avoided.[2,7,8]

Van Zee et al., from Memorial Sloan-Kettering Cancer Center (MSKCC), has developed a validated nomogram model to predict the risk of non-SLN metastasis with nine influenced factors including tumor size, tumor type and nuclear grade, lymphovascular invasion (LVI), multifocality, estrogen receptor (ER) status, the number of negative SLNs, the number of positive SLNs, pathological tumor size, and detection method of SLN metastasis.[7] According to this nomogram model, it has been well accepted and validated only in Western countries. However, it is still unknown and not well established in Asian population with some differences in clinical characteristics and pathological subtypes. Moreover, there are few result studies in China, Taiwan, and Japan, especially in Thailand where the nomogram has never before been implied.[9-11]

Hence, the aim of this study is to validate the MSKCC nomogram to predict the likelihood of non-SLN metastasis after SLN positive in Thai population, and to evaluate the relationship between variability of clinicopathologic factors and non-SLN metastasis to avoid unnecessary ALND.

Materials and Methods

Study patients

This study was approved by the Ethic Committee of Phramongkutklao Hospital and College of Medicine. The data collection was obtained between January 2012 and December 2018. The inclusion criteria were primary invasive breast carcinoma with clinical node negative axilla and no prior systemic treatment, successful SLN biopsy in which metastatic disease was identified, and completion of ALND.

SLN biopsy and pathological evaluation

Intraoperative lymphatic mapping was performed by periareolar or peritumoral injection. Isosulfan blue dye was used and left for 10 minutes to allow the dye to stain on targeted node group. Intraoperative frozen section was done on all SLNs. The SLN was cut longitudinally into 2 halves, then sectioned at 2-3 mm interval, and stained with hematoxylin and eosin (Routine H&E). Immunohistochemical staining was not routinely used in the diagnosis of SLN metastasis.

The size of metastasis tumor deposits within all nodes was categorized as 1) isolated tumor cells (ITC) with tumor deposit of 0.2 mm or less (pN0i+), 2) micro-metastases (MI) with tumor deposit of greater than 0.2 mm and/or more than 200 cells but not greater than 2 mm (pN1mi), and 3) macro-metastases with tumor deposit greater than 2 mm (pN1).

If frozen SLN was positive, the complete ALND was done immediately. All SLNs and specimens from ALND were fixed in formalin and embedded to obtain permanent sections by routine H&E technique.

MSKCC nomogram and Clinicopathological characters

The Memorial Sloan-Kettering nomogram is a computerized model used for estimating the probability of non-SLN metastasis. This nomogram is based on nine clinical and pathological variables and additional factors including: patient age, tumor size (pathological size of invasive carcinoma), tumor type (ductal or lobular

carcinoma) and nuclear grade, multifocality, presence of LVI, estrogen receptor (ER), progesterone receptor (PR), Human epidermal growth factor receptor 2 (HER -2) status, positive SLN, negative SLN, positive non-SLN, negative non- SLN, and type of metastasis.

Statistical analysis

The Chi-square test for categorical variables and t-test for continuous variables were used for comparing the difference in characteristic variables between MSKCC and our study. Firstly, MSKCC nomogram was used for calculating the probability of additional non SLN metastasis in 92 Thai breast cancer patients with positive SLN biopsy. The validity of nomogram was evaluated with the area under a receiving operative characteristic (ROC) curve (AUC) with 95% confidence interval (95%CI). The ROC curve showed the relationship between sensitivity and false positive rate (1-specificity) of a test across all the possible threshold values indicating the presence of a disease. The area under the curve (AUC) is a summary measure of the ROC. Multivariate logistic regression analysis was performed to determine predictors related to the non-SLN metastasis. Data analyses were done using SPSS 17.0.

Results

Ninety two patients were included in our study. Of these, 52 (56%) had additional positive non-SLN. The descriptive characteristics of study population were shown in Table 1. The differences, when compared with the MSKCC study, included tumor size, tumor type and nuclear grade, multifocal method of SLN detection, and the number of negative SLN.

Ductal grade III, the number of positive SLN, the number of negative SLN, presentation of LVI, multifocality, and HER-2 positive 3+ were related to non-SLN metastasis by univariate analysis. However, multivariable logistic regression analysis showed that lymphovascular invasion ($p < 0.001$), multifocality ($p = 0.002$), and HER-2 positive 3+ ($p = 0.018$) were independent predictors for non-SLN metastasis (Table 2).

The predictive accuracy of MSKCC nomogram in our collective patients and the area under the receiving operating characteristics curve (AUC) was 0.78 (95%CI: range 0.688-0.877) versus 0.76 in MSKCC study. (Figure 1)

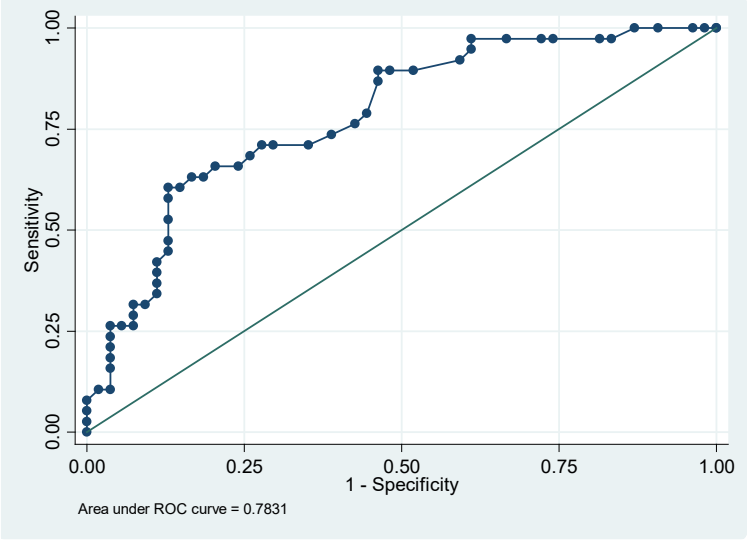

Figure 1 Discrimination of the Memorial Sloan-Kettering Cancer Center (MSKCC) nomogram for predicting the risk of positive non-sentinel nodes in Thai breast cancer patients (The area under the receiver operating characteristics (ROC) curve in our study population = 0.78 (95%CI: 0.688-0.877).

Table 1 Descriptive characteristics of patient population

Variable	MSKCC n = 373		Our study n=92		*p*-value
	n	%	n	%	
Age(years)					
≤50	157	421	38	41.3	0.891
>50	216	579	54	58.7	
Pathological size (cm)					
<= 0.5	13	35	1	1.1	0.003*
0.6-1.0	49	131	4	4.3	
1.1-2.0	166	445	33	35.9	
2.1-3.0	93	249	31	33.7	
3.1-5.0	41	11	21	22.8	
>5.1	11	29	2	2.2	
Tumor type and nuclear grade					
Ductal,I	11	2.9	19	20.7	< 0.001*
Ductal,II	175	46.9	40	43.5	
Ductal,III	129	34.6	31	33.7	
Lobular	58	15.5	2	2.2	
Lymphovascular invasion					
No	219	58.7	45	48.9	0.089
Yes	154	41.3	47	51.1	
Multifocal					
No	241	64.6	78	84.8	< 0.001*
Yes	132	35.4	14	15.2	
Estrogen-receptor status					
Negative	83	22.3	29	31.5	0.063
Positive	290	77.7	63	68.5	
Method of detection					
IHC	18	4.8	0	0	< 0.001*
Serial	40	10.7	0	0	
H&E Routine	23	6.2	0	0	
H&E Frozen	273	73.2	92	100	
Frozen sections not done	19	5.1	0	0	

Table 1 Descriptive characteristics of patient population (continue)

Variable	MSKCC n = 373		Our study n=92		*p*-value
	n	%	n	%	
Positive SLN (n)					
1	265	71	62	67.4	0.492
2	75	20.1	19	20.7	
3	21	5.6	7	7.6	
4	8	2.1	1	1.1	
>= 5	4	1.1	3	3.3	
Negative SLN (n)					
0	132	35.4	9	9.8	< 0.001*
1	79	21.2	21	22.8	
2	72	19.3	32	34.8	
3	41	11.1	22	23.9	
4	22	5.9	6	6.5	
>= 5	27	7.2	2	2.2	
PR					
Negative			53	57.6	
Positive			39	42.4	
HER2					
Negative			40	43.5	
1+			15	16.3	
2+			19	20.7	
3+			18	19.6	

MSKCC Memorial Sloan-Kettering Cancer Center, IHC immunohistochemistry, H&E hematoxylin and eosin, SLN sentinel lymph node, HER-2 Human epidermal growth factor receptor2

Table 2 Multivariate analysis of factors related with non-SLN metastasis

Variable	Odd ratio (95%CI)
Tumor size	1.157
Tumor type and nuclear grade	
- Ductal, grade I	Reference
- Ductal, grade II	0.713
- Ductal, grade III	0.985
- Lobular	N/A
Positive SLN	2.599
Lymphovascular invasion	4.354*
Multifocal	20.182*
ER	1.227
PR	1.700
Her-2	
- Negative	Reference
- 1+	0.320
- 2+	3.268
- 3+	7.123*

Discussion

Axillary lymph node status is one of the important prognostic and predictive factors for breast cancer. SLN biopsy was firmly established worldwide for routine practice in breast cancer during the end of the 1990s.[4,7,12,13] Negative SLN biopsy could be proved to protect nearly half of all patients from unnecessary ALND. In case of positive SLN, a complete ALND is still a standard therapy. However, many studies revealed that 40% to 70% of positive SLN metastasis has no residual disease in additional non-SLN nodes after ALND.[3-7] These patients not only would receive no benefit from ALND but also might have ALND complications such as seroma, lymphedema, arm paresthesia, and chronic pain. During recent years, they have been re-assessing for tradition mode through the study of axillary node metastasis. According to the American college of Surgeons Oncology group (ACOSOG) Z0011 trial, it was concluded after the median follow up of 6.3 years that there is no significant difference in loco-regional recurrence and overall survival in those with and without ALND.[5,3]

As the earliest model, the prospective MSKCC study of 373 patients showed the AUC of 0.76.[7] This nomogram has been validated by worldwide centers and the value of the AUC ranged from 0.58 to 0.86.[8,13-17] Most validation studies were from Western countries. Therefore, we reviewed the studies in Asian population (Table 3).

The tumor hetergenousity characteristics of breast cancer in Asian population differ from those in the Western countries. The important factors, including tumor size, tumor type and nuclear grading, multifocality, method of SLN detection, and negative SLN, can lead to changes in predicting accuracy. The great difference SLN mapping technique in our hospital could be detected by injection of blue dye alone, not the combination. Also, the detection of SLN metastasis is only done by frozen section. Lambert et al suggested Touch imprint cytology (TIC) as an accurate tool for better detection of SLN metastasis.[21] However, Kocsis et al. in the same way found that both methods could yield similar results.

Univariate analysis of our study showed ductal grade III, the number of positive SLN, the number of

Table 3 Review the literature of the validated of MSKCC and the value of the AUC

Authors	Country	Year	Patients with positive SLN	AUC
Cho et al.[18]	Korea	2008	82	0.786
Tan et al.[19]	Singapore	2011	60	0.6938
Sasada et al.[20]	Japan	2012	116	0.73
Kuo et al.[9]	Taiwan	2013	324	0.738
Chue et al.[10]	Singapore	2014	266	0.716
Liu et al.[11]	China	2014	120	0.688

negative SLN, presentation of LVI, multi-focality and HER-2 positive3+ as related to non-SLN metastasis. After multivariable logistic regression analysis, it showed that lymphovascular invasion ($p < 0.001$), multifocality ($p = 0.002$), and HER-2 positive 3+ ($p = 0.018$) were three independent predictors for non-SLN metastasis, whereas HER-2 status was the additional factor we collected to identify tumor subtype and prognosis. In this study, we found that it is one variable factor related to non-SLN metastasis.

Furthermore, the size of SLN involvement has been mentioned as a significant predictor of non-SLN metastasis in some studies, but not in the MSKCC nomogram. Weiser et al. reported that patients with metastasis ≤ 2 mm in SLN have very low risk of non-SLN metastasis.[22] Meanwhile, Kohrt et al. used the size of SLN metastasis as one of the three factors in the Stanford Online Calculators (SOC). Moreover, many studies have validated this model with good results.[13]

Finally, we believe that radical disparities and differences in research methods between our study and the MSKCC model are factors leading to inconsistency of results. To our knowledge, we are the first to report the validation of MSKCC nomogram in Thai breast cancer patients. The ROC curve and AUC value in our patients was 0.78, indicating that the MSKCC nomogram could provide a reliable prediction method for Thai breast cancer patients.

Conclusion

MSKCC nomogram can be widely applied as a useful tool to predict the probability of non-SLN metastasis in Thai breast cancer. By the use of nomogram, physicians should validate a suitable nomogram for each patient population. The assessment of clinical status and nomogram analysis could reduce the use of unnecessary ALND.

Disclosure

The authors have no conflicts of interest in this study.

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