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THE PREDICTIVE PROBABILITY OF TWO DIFFERENT BREAST CANCER NOMOGRAMS FOR NON SENTINEL AXILLARY LYMPH NODE METASTASIS IN POSITIVE SENTINEL LYMPH NODE BIOPSY

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ABSTRACT

INTRODUCTION: Non sentinel axillary lymph node metastasis (NSLNM) occurs in 35-50% of breast cancer (BC) patients having positive sentinel lymph nodes (SLN). A nomogram which includes 8 variables was developed at Memorial Sloan Kettering Cancer Center (MSKCC) in 2003 and it has been validated at sources outside that institution. The Stanford University group recently reported their nomogram which evaluated 3 variables.

AIM: The aim of this study is to evaluate the predictability of two different scoring systems wherein 3 or 8 variables are used in the same patient groups.

MATERIALS and METHODS: We identified 201 patients who had a positive SLN biopsy and completion axillary lymph node dissection at Magee-Womens Hospital of UPMC over a 5 year period. The computerized BC nomograms developed by MSKCC and Stanford University were used to calculate the probability of non-sentinel lymph node metastases. Area Under (AUC) Receiver Operating Characteristics Curve (ROC) was calculated for each nomogram and the values more than 0.70 have been accepted that presents considerable discrimination.

RESULTS: Sixty-six of 201 patients (32.8%) had positive axillary NSLNM. The mean predicted probability of positive NSLNM was 25.4% (3-93), and 66.3% (7-100) for the MSKCC and Stanford nomograms, respectively. The AUC values were 0.73 and 0.67 for MSKCC and Stanford nomograms, respectively.

DISCUSSION and CONCLUSION: Nomograms for predicting the probability of NSLNM in BC patients have been in use for 5 years. It is clear there are discrepancies in the results of nomograms among the studies using the same scoring system. Notwithstanding the Stanford nomogram is easier to implement as it considers only 3 variables in our study, we found the MSKCC nomogram to be more predictive than the Stanford nomogram Nomograms developed at outside institutions should be used with caution when counseling patients regarding the risk of additional nodal disease.

Key words: breast cancer, sentinel lymph node, nomogram

SENTİNEL LENF DÜĞÜMÜ BİOPSİSİ POSİTİVE OLAN HASTALARDA NON SENTİNEL LENF DÜĞÜMLERİNİN DURUMUNU ÖNCEDEN TESPİT ETMEDE İKİ FARKLI MEME KANSERİ NOMOGRAMININ ÖNEMİ

ÖZET

GİRİŞ: Sentinel lenf düğümü (SLD) biyopsi sonucu pozitif olan meme kanserli (MK) hastaların, %35-50'sinde nonsentinel lenf düğümü metastazı (NSLDM) tespit edilir. Memorial Sloan Kettering Cancer Center (MSKCC) tarafından 2003 yılında 8 değişkenin değerlendirildiği bir nomogram geliştirilmiştir ve bu nomogram başka merkezler tarafından da kullanılmıştır. Yakın zamanda Stanford Üniversitesi tarafından, 3 değişken kullanan yeni bir nomogram geliştirilmiştir.

AMAC: Bu çalışmanın amacı 3 ve 8 değişken kullanan iki farklı nomogramın aynı hasta grubundaki etkinliğini araştırmaktır.

MATERYAL ve METOD: UPMC Magee-Womens Hospital'da 5 yıllık periyodda SLD positive olup tamamlayıcı aksiller diseksiyon yapılan 201 MK'li hasta tespit edildi. Hastaların NSLD metastazı ihtimallerinin hesaplanması icin MSKCC ve Stanford üniversitesi tarafından hazırlanan ve internet üzerinden uygulanan formüller kullanıldı. Her iki nomogram icin "Receiver Operating Characteristics (ROC)" eğrileri oluşturulup ve eğriler altındaki alanlar (AUC) hesaplandı. AUC değeri 0.70 ve üzerinde hesaplanan yöntem etkin olarak kabul edildi.

SONUÇLAR: İkiyüzbir hastanın 66'sında (%32.8) NSLDM saptandı. NSLNM oranları MSKCC nomogramına göre ortalama %25.4 (3-93) ve Stanford Üniversitesi nomogramına göre ortalama %66.3 (7-100) olarak saptandı. AUC değerleri MSKCC nomogramı icin 0.73 Stanford üniversitesi nomogramı için 0.67 olarak hesaplandı.

TARTIŞMA ve SONUÇ: MK hastalarında NSLDM belirleyebilmek için nomogramlar son 5 yıldır kullanılmaktadır. Aynı nomogramı kullanan değişik çalışmalarda farklı sonuçlar tespit edilmiştir. Hernekadar Stanford nomogramı 3 değişken kullandığı için uygulanması daha kolay ise de bizim çalışmamızda MSKCC nomogramı Stanford Üniversitesi nomogramına göre daha etkin bulunmuştur. SLD dışındaki aksilla tutulma olasılığını önceden değerlendirip buna göre tedavi planlanırken, başka merkezlerde geliştirilen nomogramlar dikkatli kullanılmalıdır.

Anahtar sözcükler: meme kanseri, sentinel lenf düğümü, nomogram

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Axillary surgery is an important part of breast cancer (BC) surgery, since axillary lymph node metastasis is one of the most important prognostic factors in BC patients. Sentinel lymph node (SLN) biopsy has been becoming a standard axillary approach for clinically axillary negative BC patients in last ten years. Completion axillary lymph node dissection (CALND) is performed if the patient has involved SLN. Non SLN metastasis (NSLNM) is detected in 35-50% of the SLN positive BC patients (1,2). Several studies have investigated many predicting parameters to avoid unnecessary CALND in SLN positive patients (1-5). Some authors described formulations which are called breast nomograms for more accurate estimation of NSLNM in SLN positive BC patients.

The first acceptable nomogram was published by Van Zee et al. from The Memorial Sloan Kettering Cancer Center (MSKCC) in 2003 (6). MSKCC nomogram was internationally accepted and commonly used to predict NSLNM. The predictability of MSKCC nomogram was attempted with prospective study but several trials showed the limitation of the nomogram (7-11). The nomogram is limited as it has eight variables and not applicable if one of the parameters is unavailable.

The new nomogram was published from the Stanford University recently (12). This nomogram is simple than MSKCC nomogram and using only three factors rather than eight factors of MSKCC.

The present study aimed to evaluate predictibility of two different nomograms about NSLNM in SLN positive BC patients in our department.

Material and methods

We reviewed retrospectively the patients who underwent SLN biopsy at Magee-Womens Hospital of The University of Pittsburgh Medical Center between December 1999 and December 2005. Two hundred thirty three patients were identified with positive SLN biopsy and were operated on completion ALND. Thirty-two patients who have been had primary chemotherapy were excluded from the study. The pathologic findings of the remaining 201 patients are evaluated.

The variables used included the pathologic size of the tumour in centimetres, nuclear grade and tumour type [ductal carcinoma (DC) grade I, DC grade II and DC grade III or lobular carcinoma], the number of positive SLNs, the number of negative SLNs, the method of detection of SLNs [frozen section (FS)], routine haematoxylin–eosin (HE), serial section haematoxylin–eosin (SSHE) and immunohistochemistry (IHC), oestrogen receptor status, lympho-vascular invasion, the largest size of SLN metastasis in milimeter (also micrometastasis or macrometastsis) and multifocality of the tumour. All patients underwent SLN biopsy using blue dye, radioactive colloid or both, this technique described by Breslin et al. (13). SLN were evaluated with HE section, SSHE and IHC. FS was performed on SLN(s), suspicious on gross examination. Routine HE and IHC were done for NSLNM. If any of the eight parameters was unknown, patient was not included in the study. The total

Table 1. Descriptive characteristics of study group (n=201)

Characteristics of the patients	*n (%)*
Age (year)	
≤ 50	80 (39.8)
>50	121 (60.2)
Pathologic tumor size (cm)	
<2	106 (52.7)
85 (42.2)	
5<	10 (5.1)
Tumor type and Nuclear Grade	
Ductal, 1	9(4.4)
Ductal, 2	88 (43.7)
Ductal, 3	77 (38.3)
Lobular	27 (13.6%)
Lympho-vascular invasion	
Yes	104 (51.7)
No	97 (48.3)
Estrogen Receptor status	
Positive	172 (85.5%)
Negative	29 (14.5)
SLN detection method	
IHC	86 (42.8)
SSHE	24 (11.9)
Routine HE	91 (45.3)
Frozen done	68 (33.8)
Frozen not done	133 (66.2)
Number of positive SLN	
1	148 (73.7)
2	38 (19.0)
3	10 (5.0)
4	2 (0.9)
≥5	3 (1.4)
Number of negative SLN	
0	61 (30.4)
1	65 (32.4)
2	38 (19.0)
3	20 (9.9)
4	14 (6.9)
≥5	3 (1.4)
Proportion of positive SLN/total SLN	
<0.5	65 (32.3)
0.5≤-<1	75 (37.3)
1	61 (30.4)
Micrometastasis	
Yes	55 (27.4)
No	146 (72.6)

(SLN, sentinel lymph nod; IHC, immunohystochemistry; SSHE, serial section haematoxylin-eosin, HE; haematoxylin-eosin)

Table 2. Predicted probabilities of patients according to the scoring systems

MSKCC	25.4 % (3-93)
Stanford	66.3 % (7-100)

MSKCC; Memorial Sloan Kettering Cancer Center. Actual proportion is 32.8%.

Table 3. The measured AUCs for nomograms

MSKCC	0.73*
Stanford	0.67

*The result higher than expected (0.70)
MSKCC, Memmorial Sloan Kettering Cancer Center

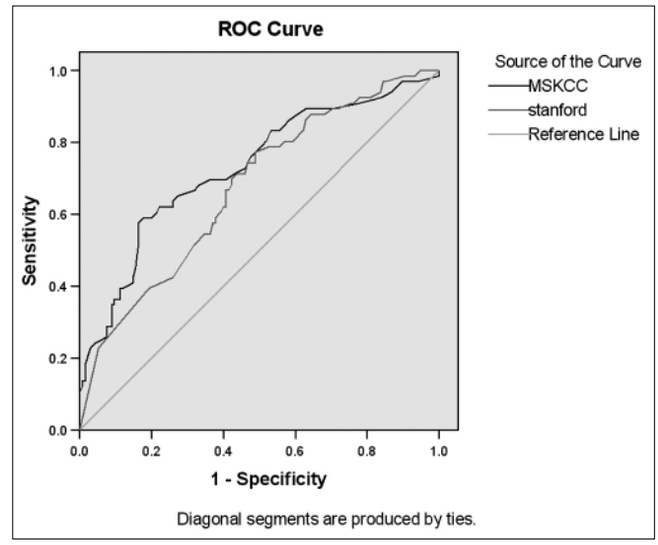

Figure 1. The ROC curves of nomograms

number of resected axillary lymph nodes and the number of NS-LNM have been reviewed also for all patients. .

Analysis

The risk assesments of all patients were calculated with two different methods. The calculation according to MSKCC nomogram was done by using of free online version (www.mskcc.org/nomograms). Tumor size, grade, number of positive SLNs, number of negative SLNs, the method of detection of SLNs, estrogen receptor status, lymphovascular invasion status and multifocality of the tumor have been used for this nomogram.

The nomogram which has been published recently was used for the calculation (12). The tumor size, the status of lympho-vascular invasion and the largest size of metastasis have been used and the calculation was done by using of online version of this method (http://www-stat.stanford.edu/~olshen/NSLNcalculator/).

Statistical analysis

The mean predicted probability from the two nomograms for same patient group was compared with the actual proportion, and the discrimination of the nomograms was assessed by calculating the area under (AUC) the receiver operating characteristic (ROC) curve. It is generally accepted that AUC values 0.7–0.8 represent considerable discrimination, whereas the AUC values exceeding 0.8 represent good discrimination (14).

Results

Two-hundred-one patients were underwent SLN biopsy followed by CALND from December 1999 to December 2005 in our department because of metastatic SLN. The mean age was 54.1 (30-82) years and 60.2% of the patients were older than 50 years (Table 1). The mean tumor size was 2.11 (0.5-7.3) cm. The 13.6% of tumors were lobular carcinoma. Multicentricity was present in 31.8% (n=64) of the patients. The mean SLN number was 2.75 (1-11) and the mean involved SLN number was 1.38 (1-7). There were 55 (27.4%) micrometastasis in involved SLNs and the mean OMS was 9.8 mm (2-35). Sixty-six patients (32.8%) had positive axillary NS-LNM. The number of dissected axillary lymph node was 15.5 (1-50) averagely and the number of involved NSLNM was 1.3 (0-47).

The mean predicted probability of the patients was 25.4% (3-93) and 66.3% (7-100) for MSKCC and Stanford nomograms respectively (Table 2).

The AUC values were 0.73 and 0.67 for the MSKCC and the Stanford nomograms, respectively (Figure 1 and Table 3).

Discussion

The BC surgery is becoming more conservative to avoid unnecessary patient morbidity. Axillary surgery in BC is more important because of the staging of the cancer and decision making of adjuvant treatment of the patient. The current paradigm, for nodal spreading of cancer, is the cancer cells spread firstly to SLN and then to non SLNs (15). Thus CALND can be avoided in SLN negative tumors but CALND is the standard management if the SLN is positive for metastatic disease. However 65-50% of the SLN involved patients have not further axillary metastasis, therefore axillary dissection could be avoided for these patients (1,2,6,12,15,16).

MSKCC (6) created a nomogram in 2003 to predict of axillary NS-LNM in the patients who had involved SLNs. They found the rates of NSLNM as 38% and 40% for patients who older than 50 years old and younger than 50, respectively. There were retrospective group and prospective group in Van Zee's study. AUC was 0.76 for retrospective study group and was 0.77 for prospective study group in that study. In our study AUC of the MSKCC's nomogram was 0.73.

The MSKCC nomogram was validated with several studies in the world (8,11,16-18) including our department, before (19). But other studies concluded that the MSKCC nomogram has limitations because the missing pathologic findings could affect the nomogram application (7,10). On the other hand the results from European institutions are heterogeneous such as Smidt from Netherland and Ponzone from Italy (11,20) were validated the MSKCC nomogram for prediction of NSLNM, but Kocsis from Hungary found it is weak for prediction of NSLNM with the MSKCC nomogram in their population (7). Pal from UK applied the MSKCC nomogram to their patients and found the AUC value as 0.68 (15). Zgajnar from Slovenia (21) reported that the MSKCC nomogram overestimates the probability of NSLNM and Klar from Germany (10) concluded that, the MSKCC nomogram did not provide a reliable predictive model for identifying patients with a low or a high risk for NSLNM. According to Alran et al (France) (9) practitioners must be aware of using the MSKCC nomogram in patients with micrometastatic SLN. In Alran's study, which validated the MSKCC nomogram, 35% of 588 patients had micrometastasis and the nomogram could not be able predict the NSLNM in this group of patients. Conversely, the rate of micrometastasis in Kohrt's study (12) group was approximately 93% and the MSKCC nomogram was validated with AUC value of 0.77. Van Zee et al (6) did not use the size of SLN metastasis in their study as a predictive parameter. They stated that this was a limitation of their study but they also emphasized that the measuring of the size of metastastasis was misleading because some nodes might have scattered single cells or multiple small clusters of cells. According to authors, an accurate estimate of volume could be assigned to each SLN metastasis. However, this is extremely time-consuming and somewhat impractical.

There were two centers' data in Stanford's study (12). They used the Bay Area SLN Study for Detection of Axillary Metastasis in Breast Cancer data (BAD) and Northwestern Memorial Hospital in Chicago, IL, data for the study (NMD). NSLNM rate was 35.4% in 285 patients of BAD and 31.0% in 77 patients of NMD. When they applied the MSKCC nomogram to the two groups they found the AUC 0.77 and 0.62 for BAD and NMD, respectively. According to their own nomogram the AUCs were 0.83 and 0.77 for BAD and NMD, respectively. In our study the AUC value for the Stanford nomogram was 0.67 and it was lower than the expecting value of 0.70.

In the Stanford study only 7% of patients with positive SLN had macrometastsis in BAD. The rate of macrometasis in positive SLN was 56% in NMD. The rate of macrometastasis in our study was approximately 25% and similar with Van Zee study group (6). In the Stanford study (12) the rate of macrometastasis was lower than our study group.

The rate of the patients with T1 tumor (<2cm) was 50% in the Stanford study (12) and this rate similar with our study group and Van Zee (6) study group. However, lymphovascular invasion rates have discrepancy in Stanford study. Lymphovascular invasion was unknown 25% of the patients in BAD, but lymphovascular invasion were positive in 67% of the patients in NMD. In our study 50% of the patients had positive lymphovascular invasion, and we think that the difference of the rates of lymphovascular invasion and micrometastastasis between Stanford study group and our study, were the reasons of inaccuracy of the Stanford model.

In conclusion, the BC patients who had metastatic SLNs should be informed the predictive probalility of NSLN metastasis and some patients may prefer to avoid CALND by using of the nomograms. MSKCC nomogram is most validated system on this issue but the Stanford nomogram is easier to implement as it considers only 3 variables. However, we found the MSKCC nomogram to be more predictive than the Stanford nomogram. Nomograms developed at outside institutions should be first validated before applying them to the clinical practice and should be used with caution when counseling patients regarding the risk of additional nodal disease.

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