

Validation of Memorial Sloan Kettering Cancer Center nomogram to detect non-sentinel lymph node metastases in a United Kingdom cohort

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SUMMARY: Validation of Memorial Sloan Kettering Cancer Center nomogram to detect non-sentinel lymph node metastases in a United Kingdom cohort.

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Aim. Axillary lymph node dissection, although associated with long-term morbidity, has been the standard of treatment for all node-positive breast cancer patients. We assessed the risk prediction ability (validity) of Memorial Sloan Kettering Cancer Center (MSKCC) nomogram for non-sentinel lymph node metastases and analysed the outcome of patients with sentinel node metastases.

Patients and methods. All operable early breast cancer patients with sentinel node macro metastases (size > 2mm) who underwent axillary dissection from April 2009 to March 2015 were considered eligible. The risk of non-sentinel lymph node metastases was calculated

using an online MSKCC calculator, and accuracy was determined based on the area under the receiver-operating characteristic curve (AUC-ROC). Tumour characteristics and overall survival were also analysed as secondary end points.

Results. Of 1745 patients who were diagnosed with operable breast cancer during the study period, 114 patients were considered eligible. The AUC-ROC was 0.66 suggestive of lesser accuracy in prediction and not statistically significant (p value = 0.7303). Seventy-six (50.7%) of these patients did not have any non-sentinel node metastases. At a mean follow up of four years, the disease-free survival was 86.4% and overall survival rate was 88.4%.

Conclusions. The MSKCC nomogram was unable to accurately predict the risk in our cohort of patients with more than half of this cohort of patients not requiring axillary dissection. These findings are consistent with other European studies. This study thus highlights the need for modified prediction model for European cohorts.

KEY WORDS: Nomogram - Sentinel node biopsy - Breast cancer - Axillary dissection.

Introduction

Axillary lymph node dissection has been the traditional standard of care for breast cancer patients with nodal metastases (1-3). Nodal metastases are very rarely diagnosed clinically and are generally identified by axillary ultrasound with fine needle aspiration cytology or core biopsy of the suspicious axillary lymph nodes (4-6). For patients with normal axillary ultrasound, sentinel lymph node biopsy (SNB) is performed to confirm nodal metastases.

Once nodal metastases are identified either via axillary ultrasound or SNB, axillary lymph node dis-

section is performed to achieve local disease control (7, 8). This technique also provides accurate nodal status to inform the decision to provide radiotherapy to the supraclavicular region and influences decisions on administering systemic therapy (9, 10).

An increased understanding of tumour biology in recent years has suggested that other patient- and tumour-related factors should also influence the decision to treat patients with systemic therapy (11, 12). In addition, early cancer detection by screening mammograms leads to early management and reduced tumour nodal involvement (13, 14). Also in certain patients, adjuvant systemic treatment is needed despite no lymph nodal involvement (15). These concepts in addition to the fact that axillary lymph node dissection is associated with unacceptable risks of complications (16-18) (seroma, infection, paraesthesia, shoulder pain, weakness and lymphedema) has raised

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questions as to the need for complete axillary lymph node dissection in all patients with positive sentinel node biopsies (19).

A variety of approaches have evolved in recent years to identify groups of low-risk patients who could safely avoid axillary lymph node dissection. The American College of Surgeons Oncology Group (ACOSOG) demonstrated in the Z0011 trial that certain groups of patients can safely avoid lymph node dissection without affecting local control or survival (20, 21). These groups of patients have early stage breast cancer with tumour sizes less than 5 cm and have undergone lumpectomy with sentinel biopsy. If they have clear margins and one or two positive nodes without extra nodal extension or matting, they could forego axillary lymph node dissection provided they are treated with whole breast radiation postoperatively. Although it was considered as a practice changing trial, the selection bias, difficulty in applying this treatment to younger patients and those with invasive lobular disease and the use of tangential field radiation associated with the trial, limits the true clinical significance of these findings (18-20). Systemic review and meta-analysis by Ram et al. (22) was unable to conclude favourably to avoid completion axillary node dissection on sentinel node macro metastases. There is currently a trial (23) in the United Kingdom, recruiting patients to identify subgroup of patients with 1 or 2 nodal metastases who could avoid axillary dissection.

Different prediction models have also been published to identify the risk of non-sentinel lymph node metastases (24). If patients have a low score, suggesting that they are unlikely to have non-sentinel node metastases, axillary lymph node dissection is avoided. A review of these models indicated that the Memorial Sloan Kettering Cancer Center (MSKCC) model (25) is robust despite some limitations (26, 27). This model was validated by a total of 373 cases and the area under the receiver-operating characteristic curve (AUC) was 0.77, which proved to have a good diagnostic value.

The primary aim of our study was to apply the tumour characteristics in the MSKCC nomogram and assess the risk prediction of non-sentinel node metastases in a United Kingdom cohort. We also analysed the clinical and pathological outcomes of breast cancer patients who underwent axillary lymph node dissection after positive SNB.

Patients and methods

All breast cancer patients who underwent SNB after meeting the criteria (histologically proven breast cancer, negative axillary lymph nodes on palpation and sonography) were included in the study from the surgical database of Southend University Hospital.

For SNB, we used either blue dye technique or the combined technique using radio-isotope. Both techniques have been described elsewhere in detail (28). For blue dye technique, Patent Blue V was injected subdermally in the periareolar region in the upper outer quadrant of the cancerous breast prior to surgery. For combined technique, ^{99m}Tc -nanocol was injected at the same place 3 to 5 minutes prior to the injection of blue dye. Intraoperatively, the sentinel lymph nodes (SLN) were detected by the appearance of blue node in the former procedure and the signal is detected (hot) using a hand-held gamma probe along with blue node in the latter procedure and sent for pathological evaluation by haematoxylin-eosin staining (H&E) and immunohistochemistry (IHC).

Sentinel node is considered negative even if there are isolated tumour cells and /or micro metastases (less than 2mm in size) and considered positive if they are more than 2mm in size by standard nodal assessment or if there are any extra capsular spread on micro metastasis. Patients with positive sentinel lymph node biopsies were discussed in the multi-disciplinary meeting and offered level II and, or level III axillary dissection provided no significant medical comorbidities were noted. Details regarding positive SNB and further axillary lymph node dissection were obtained from histopathological reports. Demographics and tumour characteristics were identified from multi-disciplinary discussions. Clinical letters were used to identify the follow-up of these patients, including any significant events.

All analyses were conducted with The Graph Pad software (Prism version 5). For numeric data, values are expressed in median with percentages. Numeric data were analysed with Student's-t-test if normal distribution and categoric data, with the Chi-Square-test or with Fisher's exact test.

The MSKCC nomogram is a validated model to estimate the predictive value of the involvement of additional non-sentinel lymph node metastases. The nomogram is accessed at <http://nomograms.mskcc.org/Breast/BreastAdditionalNonSLNMetastasesPage.a>

spx. Nine independent variables, including whether frozen sectioning was performed, pathological size, tumour type and grade, number of positive and negative sentinel nodes, method of node detection, lymphovascular invasion, multifocality and oestrogen receptors status were uploaded into the MSKCC online calculator.

Prediction scores were obtained and tabulated to construct the ROC curves, and the AUC was calculated. Further information on the methods of development and internal validation are available on the above internet site and the corresponding publication (25).

The value of the AUC is between 0.5 and 1.0. The AUC has a lower accuracy at 0.5 to 0.7 and a superior accuracy in the range of 0.7 to 0.9; the AUC has high accuracy at values greater than 0.9.

Results

Of the 1745 patients who received surgery for breast cancer from April 2009 to March 2015, 1470 patients had sentinel lymph node biopsies. 117 patients had a positive sentinel node biopsy, with a positivity rate of 8%. Three patients were excluded as two patients had neo adjuvant chemotherapy before axillary lymph node dissection and one patient declined surgery. The remaining 114 patients were considered eligible for the study.

Pathological factors of sentinel node metastases

The overall descriptive clinical and histopathological characteristics of patients with positive SLN biopsy (n = 114) are shown in Table 1. The mean and median ages were 59.5 and 61 years respectively (ranging 24 - 85). The mean and median tumour sizes were 20.6 and 21 mm respectively, ranging from 1 to 4.5 cm. Most of the tumours were invasive ductal carcinomas (93%) and of higher grades (Grade II, 53%; instead of Grade III, 48%).

Tumours in 51 patients (44.7%) were associated with lymphovascular invasion, and 107 (93.8%) tumours were oestrogen positive. Tumours were progesterone positive in 84 patients (73.7%), and Her2 was overexpressed in 11.4% of patients. Most patients had wide local excision (78.9%), radiotherapy (86.8%) and hormonal treatment (96.5%). Letrozole (65.5%) was the more frequently prescribed hormonal therapy, and more than half of the patients received chemotherapy (61.4%).

TABLE 1 - PATIENT AND TUMOUR CHARACTERISTICS OF PATIENTS WHO UNDERWENT AXILLARY LYMPH NODE DISSECTION (ALND) AFTER POSITIVE SENTINEL NODE BIOPSY.

Age (year)		
Median (range) N = 114	61 (24-85)	
< 50	21	
> 50	93	
Tumour size		
Median (range)	21 mm (4-75)	
T1 (< 20 mm)	45	
T2 (20-50 mm)	69	
Tumour type		
Ductal cancer	93	
Lobular cancer	11	
Tubular cancer	4	
Mixed	6	
Grade		
Grade I	13	
Grade II	53	
Grade III	48	
Tumour subtype		
ER positive/Her2 negative	94	
Triple negative	5	
Her2 positive	13	
Receptor status		
ER positive	107	
ER negative	7	
PR positive	84	
PR negative	30	
Lymphovascular invasion		
Present	51	
Absent	63	
Surgical management		
Wide local excision	90	
Mastectomy	24	
N stage after ALND		
N1	(1-3 nodes)	87
N2	(4-9 nodes)	25
N3	(≥10 nodes)	2
Radiotherapy	99	
Chemotherapy	70	
Hormonal Treatment		
Letrozole	72	
Tamoxifen	23	
Switch therapy	12	
Other aromatase inhibitor	3	
No treatment	4	

Most of the patients had N1 disease (87 patients, 76.3%). The median number of positive nodes detected for patients with N1 disease was 1 and 4 for those with N2 disease. The average number of nodes obtained from the sentinel lymph node biopsy was 4.3. The median number of total axillary lymph nodes identified from axillary lymph node dissection was 12 (range from 10 to 23).

Nomogram

The AUC-ROC achieved by the MSKCC nomogram when predicting the risk of non-SLN metastases was 0.5304 (Figure 1) with a 95% confidence interval of 0.3527 to 0.7080. This result was not statistically significant (p value = 0.7303).

In conclusion, the MSKCC nomogram does not provide an accurate prediction of the probability of non-SLN metastasis in our cohort of SLN-positive breast cancer patients.

Survival

At a median follow-up of 37 months (range from 9 to 65 months), four significant events were noted. One patient died during adjuvant chemotherapy, another patient died of lung metastasis 28 months after the initial treatment. Third patient died of generalised illness with no proven metastasis, and fourth

patient developed contralateral breast cancer 51 months after the initial treatment. Overall there was no axillary recurrences. The disease free survival was 86.4% and overall survival rate was 88.4%.

Non-sentinel lymph node metastasis

A total of 38 patients of the 1470 patients (2.6%) showed non-SLN metastasis. The prevalence of non-SLN metastasis in the group of SLN positive patients was 33.3% (38 of 114 patients), with a mean number of 2.87 involved lymph nodes.

Comparing the histopathological factors by presence or absence of further non-SLN metastases as in Table 2, only tumour size ($p < 0.01$) correlated significantly with non-SLN metastasis. Tumour grade, histology, lymphovascular infiltration, type of surgery and biologic features (oestrogen and progesterone receptor status, Her2/neu expression) of the primary tumour did not correlate with the prevalence of non-SLN metastasis.

Discussion and conclusions

Sentinel lymph node biopsy has become widely accepted as the preferred method for staging node-negative breast cancer (16, 29, 30) while axillary

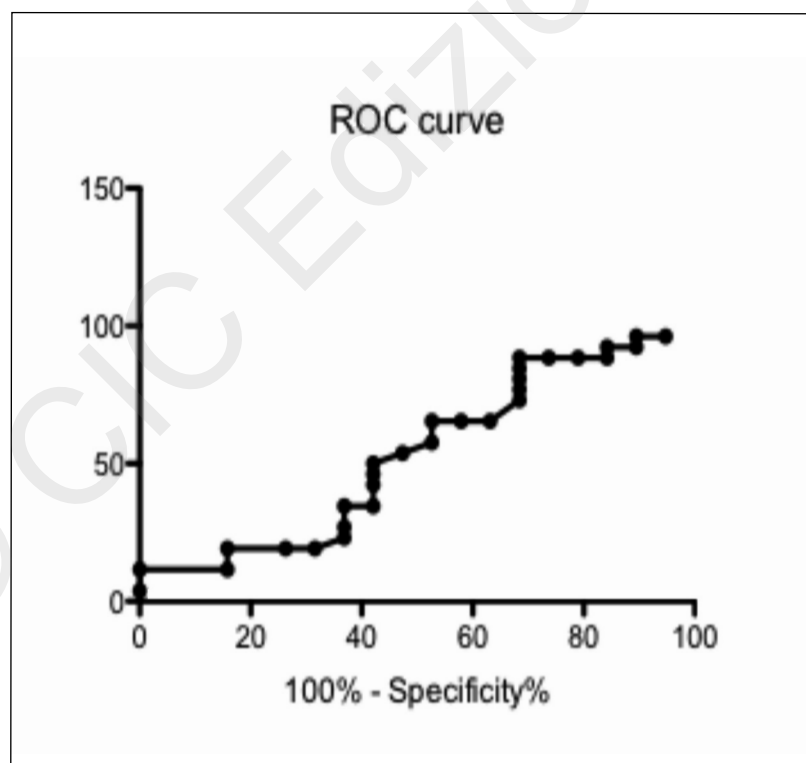


Figure 1 - The receiver operating curve (ROC) calculation for all the patients using the Memorial Sloan Kettering Cancer Center nomogram.

TABLE 2 - COMPARISON OF HISTOPATHOLOGICAL FACTORS BY PRESENCE OR ABSENCE OF FURTHER NON-SENTINEL LYMPH NODE METASTASES.

Patient characteristics	ANC 0, Positive Lymph Nodes (n=76)		ANC 1 + Positive Lymph Nodes (n=38)		p value
Age					
Median (Range)	61	(24-85)	62	(35-83)	0.11
< 50 years	14	(18.4%)	5	(13.2%)	
50-69 years	49	(64.5%)	20	(52.6%)	
≥ 70 years	13	(17.1%)	13	(34.2%)	
Type of surgery					
Breast Conserving	59	(77.6%)	29	(76.3%)	1
Mastectomy	17	(22.4%)	9	(23.7%)	
Tumour size in mm					
Median (Range)	21	(4-70)	23	(12-75)	0.01
<20 mm	34	(44.7%)	11	(28.9%)	
20-30 mm	29	(38.2%)	19	(50%)	
>30 mm	13	(17.1%)	8	(21.1%)	
MGR5 (NACH)					
Morphology of tumour					
Ductal carcinoma	62	(81.6%)	30	(78.9%)	0.62
Lobular Carcinoma	6	(7.9%)	5	(13.2%)	
Other types	8	(10.5%)	3	(7.9%)	
Tumour Grade					
Grade 1	11	(14.5%)	2	(5.3%)	0.23
Grade 2	32	(42.1%)	21	(55.2%)	
Grade 3	33	(43.4%)	15	(39.5%)	
ER status					
Negative	6	(7.9%)	1	(2.6%)	0.42
Positive	70	(92.1%)	37	(97.4%)	
PR status					
Negative	21	(27.6%)	9	(23.7%)	0.82
Positive	55	(72.4%)	29	(76.3%)	
Her2 Status					
Negative	68	(89.5%)	33	(86.8%)	0.75
Positive	8	(10.5%)	5	(13.2%)	
Triple Negative					
No	72	(94.7%)	37	(97.4%)	0.66
Yes	4	(5.3%)	1	(2.6%)	
Multifocality					
No	72	(94.7%)	37	(97.4%)	0.66
Yes	4	(5.3%)	1	(2.6%)	
Lymphovascular Invasion					
No	45	(59.2%)	18	(47.4%)	0.23
Yes	31	(40.8%)	20	(52.6%)	

lymph node dissection is recommended in patients with a positive sentinel node biopsy. However, with the changing trend in breast cancer surgery towards conservative approach, axillary lymph node dissection

is considered by many studies as overtreatment. This is partly because only 50% of the patients with metastatic disease have further axillary metastases (31), as shown in our study where only 43.3% of the

patients do have additional lymph nodal metastases. Therefore completion axillary lymph node dissection serves no therapeutic purpose in the remainder of the patients and more importantly cause significant morbidities (17, 18).

To overcome this tendency to over-treat, various tools have been identified to predict the risk of additional positive axillary nodes (non-sentinel) after positive SNB. If the risk prediction score is low (less than 10%), patients can safely avoid axillary lymph node dissection. The risk of non-sentinel metastases correlates with the size of the primary tumour, size of the metastases, number of sentinel nodes involved, lymphovascular invasion and extra nodal tumour extension (32, 33). These prognostic characteristics are incorporated in the prediction models to predict the risk of non-sentinel metastases. Of those prediction models, the MSKCC model is one of the more valid nomograms in various populations. Hence, we applied our data to this model to identify the risk of additional nodal involvement by drawing the ROC curve and calculating the AUC. The value of the AUC in our study was 0.530, which indicates lower accuracy in predicting the involvement of additional lymph nodes.

Literature review depicts the validation results from different studies were heterogeneous with more accuracy obtained in American and Australian studies and mixed results in European studies. Van Zee et al. (n=373) (25), from MSKCC obtained the ROC of 0.76, Degnim et al. (n= 89) (34) and Cripe et al. (n=92) (35) in USA obtained 0.86 and Soni et al. from Australia (n=149) (36) achieved a ROC of 0.75. However German based study by Klar et al. (n=98) (37) achieved only 0.58 and Pal et al. (n=118) (38) from UK obtained 0.68. These low prediction score in European studies is similar to our ROC of 0.53 (n=114) which questions the recommendation of MSKCC as a worldwide prediction model. It also highlights that there are some important contributing factors other than simple geographical location for lack of reproducibility of the MSKCC model.

Firstly, method of pathological assessment of sentinel nodes varies with different studies. MSKCC model uses frozen section as method of detection of metastases whilst other American and Australian studies use imprint cytology as methods of detection. These methods could possibly identify the isolated tumour cells or micrometastasis as nodal metastases compared to the Haematoxylin and Eosin preparation which accurately classify them. This could explain the low prediction score in European studies which

do not use intraoperative frozen section or imprint cytology as a marker for metastases.

Secondly, the size of the nodal metastases is not a feature of MSKCC model. Pal et al. in his revised Cambridge model obtained the higher accuracy score of 0.84 (from MSKCC score of 0.68) adding the criteria of the size of nodal metastases. It would be therefore appropriate to include the size as one of the parameter to obtain better accuracy among different populations.

In conclusion, it is important to identify the low risk group of breast cancer patients with nodal metastases who are at a low risk of additional non-sentinel metastases (39).

However to date there are no studies or models which were able to define this group reliably although Z0011 trial looks promising to redefine the axillary management of certain group of patients.

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