Factors Influencing Non-sentinel Node Involvement in Sentinel Node Positive Patients and Validation of MSKCC Nomogram in Indian Breast Cancer Population

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Abstract Current guidelines recommend completion axillary lymphnode dissection (ALND) when sentinel lymphnode (SLN) contains metastatic tumor deposit. In consequent ALND sentinel node is the only node involved by tumor in 40–70 % of cases. Recent studies demonstrate the oncologic safety of omitting completion ALND in low risk patients. Several nomograms (MSKCC, Stanford, MD Anderson score, Tenon score) had been developed in predicting the likelihood of additional nodes metastatic involvement. We evaluated accuracy of MSKCC nomogram and other clinicopathologic variables associated with additional lymph node metastasis in our patients. A total of 334 patients with primary breast cancer patients underwent SLN biopsy during the period Jan 2007 to June 2014. Clinicopathologic variables were prospectively collected. Completion ALND was done in 64 patients who had tumor deposit in SLN. The discriminatory accuracy of nomogram was analyzed using Area under Receiver operating characteristic curve (ROC). SLN was the only node involved with tumor in 69 % (44/64) of our patients. Additional lymph node metastasis was seen in 31 % (20/64). On univariate analysis, extracapsular infiltration in sentinel node and multiple sentinel nodes positivity were significantly associated ($p < 0.05$) with additional lymph node metastasis in the axilla. Area under ROC curve for nomogram

was 0.58 suggesting poor performance of the nomogram in predicting NSLN involvement. Sentinel nodes are the only nodes to be involved by tumor in 70 % of the patients. Our findings indicate that multiple sentinel node positivity and extra-capsular invasion in sentinel node significantly predicted the likelihood of additional nodal metastasis. MSKCC nomogram did not reliably predict the involvement of additional nodal metastasis in our study population.

Keywords Breast cancer · Sentinel node positive · Non-sentinel node metastasis · MSKCC nomogram

Introduction

Axillary clearance provides information on the extent of axillary nodal involvement which continues to be a reliable indicator of prognosis and staging in breast cancer patients. However, axillary clearance is associated with morbidity including seroma, lymphedema, and shoulder dysfunction in 6 to 30 % of patients [1]. In the 1990s Sentinel lymph node biopsy (SLNB) was developed and began to be accepted as an alternative for staging axilla in clinically node negative patients [2]. SLNB has now become the standard of care in clinically node negative breast cancer patients.

Subsequent studies analyzing the SLNB series noted that in 40–70 % of patients sentinel nodes (SLN) are the only nodes to be involved with tumor without any additional non-sentinel node (NSLN) involvement [3]. These individuals undergo ALND without any therapeutic benefit or any additional prognostic information obtained and exposing them to the potential complications of axillary dissection. Identification of the patients with a low probability of NSLN metastasis can spare them of the morbidity associated with ALND. Involvement of NSLN is dependent on primary tumor and sentinel node

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characteristics and several authors have devised nomograms and scoring systems (incorporating tumor and sentinel variables) to predict the probability of NSLN metastasis. The most popular ones are Memorial Sloan Kettering Cancer Center (MSKCC) nomogram [4], Cambridge nomogram [5], Stanford nomogram [6], Tenon score [7] and MD Anderson cancer center score [8]. Of these MSKCC nomogram remains the most validated nomogram in different settings [9–16]. The results have been varying in different series but in general appear to be accurate.

In the present study we aim to assess the incidence of NSLN involvement in our patients and to identify the risk factors associated with NSLN metastasis (NSLNM). We also evaluated the accuracy of MSKCC nomogram in predicting the NSLN metastasis in our cohort of patients.

Materials and Methods

We reviewed our prospectively collected database of patients treated at our center between Jan 2007 and July 2014. A total of 334 patients with clinically T1-T3 N0 tumors underwent SLNB during this period. Axilla was considered negative by clinical examination and axillary ultrasound. All patients who underwent completion ALND after SLN positivity were included in the study. Data collected included patients characteristics, tumor characteristics [size, histologic type, grade of the lesion, lymphovascular invasion (LVI), multifocality/multicentricity, estrogen and progesterone receptor (ER/PR) status, HER2-nu status and characteristics of the SLNs and other axillary lymph nodes (number of SLNs and NSLNs involved, size of SLNs- micro/macro mets, extracapsular invasion in SLN and NSLN).

Sentinel Node Localization

Sentinel nodes were localized using a combined technique of radiocolloid and blue dye injection. Technetium 99 sulphur colloid was injected in sub-areolar region 2 to 6 h prior to surgery. At time of surgery, prior to incision 2 ml of methylene blue was injected in sub-areolar plane followed by 5 min breast massage at site of injection. A hand held gamma probe was used to guide the site of incision and dissection in axilla. Nodes with isotope count greater than 10 % of count in injection site are labelled hot nodes. All hot, blue, hot and blue nodes are dissected out and submitted for frozen section. In addition any suspicious enlarged nodes were also removed and submitted for intra-operative frozen section analysis. If sentinel nodes were found to be positive for tumor, axillary dissection was performed at same sitting. The nodes obtained from axillary clearance were submitted for routine histopathology analysis.

Statistical Analysis and MSKCC Nomogram Analysis

The statistical analyses were performed by the Statistical Package for the Social Sciences (SPSS) program, version 17.0 (SPSS Inc., Chicago, IL, USA). *P* value was considered significant when less than 0.05. The online version of MSKCC nomogram (available in <http://nomograms.mskcc.org/Breast/BreastAdditionalNonSLNMetastasesPage.aspx>) was used to calculate the predicted probability of NSLN metastasis. The probability is calculated based on eight variables namely *tumor size, tumor type and grade, number of SLN positive, number of SLN negative, method of detection of SLN, LVI presence, multifocality, ER receptor status*. The clinico-pathological variables were fed into online calculator and predicted probability (percentage score) was obtained for each individual patient. A receiver operator characteristic (ROC) curve was constructed and Area under curve (AUC) was calculated to assess the discriminative accuracy of nomogram. In general it is accepted that AUC values of 0.7 to 0.8 represent considerable discrimination and AUC > 0.8 represents excellent discrimination.

Results

Of 334 patients who underwent SLNB during the study period, 70 (20.5 %) had SLN involved by tumor. Six patients had SLN metastasis identified in final HPE after a negative report on frozen section (false negative). They did not undergo ALND subsequently and axilla was included in the radiation field. Rest of the 64 patients who underwent ALND constituted the study group. *SLN identification rate was 100 % and false negative rate was 8.5 % (6/70—3 macro metastasis; 2 micro metastasis and one isolated tumor cluster cells positive detected by immunohistochemistry)*. The median patient age was 51 and median tumor size was 2.5 cms (range 1.2 to 6.5 cms). The median number of sentinel nodes removed was 3 (range 1–10) and median number of positive SLNs was 1 (range 1–4). Eighty percent ($n = 51$) of SLN positive cases had tumor involvement limited to single sentinel node. The median number of nodes excised at ALND was 18 (range 13–40). In final HPE after completion ALND it was observed *that only sentinel nodes were involved without any additional nodal metastasis in 68.8 % ($n = 44$) of patients*. NSLN was found to be metastatic in 20 of 64 patients (31.2 %) and more than half of them (11/20; 55 %) had only one NSLN involved by tumor. The median number of metastatic NSLN was 1 (range 1–6).

By univariate *analysis extra-capsular invasion in sentinel node ($p = 0.0002$) and more than one node positive in SLNB ($p = 0.04$)* were statistically significantly associated with additional NSLN metastasis. Ratio of SLN positive by SLN harvested when greater than 0.5 (42 % in ratio > 0.5 vs

21 % in ratio < 0.5) and sentinel macro-metastasis (0 % in micro-metastasis vs. 32.7 % in macro-metastasis) showed a trend towards NSLN positivity though not statistically significant. Other factors like T size, grade of lesion, multifocality/multicentricity, LVI and ER/PR status were not statistically significantly associated with NSLN metastasis in this study. On multivariate analysis (*binary logistic regression analysis*) *extracapsular invasion in SLN* ($p = 0.0001$, *Odds Ratio* = 11.3) was significantly associated with NSLN metastasis (Table 1).

The overall clinicopathological details of the original MSKCC prospective series ($n = 373$) and our study group ($n = 64$) are compared in Table 2. Our cohort had larger tumor size ($p = 0.0002$), lower incidence of multifocal and LVI + tumors ($p = 0.0002$ and 0.001 respectively) and higher number of negative SLN ($p = 0.03$). Differences between other variables were not statistically significant. The predicted probabilities of NSLN metastasis in all patients ranged between 20 and 75 % with a mean of 40 %. The mean predicted

probability in NSLN free and NSLN metastatic group were 38.9 and 42.1 % respectively. The predictive accuracy of MSKCC nomogram measured by *area under ROC curve* was $AUC = 0.558$ (95 % *CI* 0.406 to 0.710) (Fig. 1). In 22 patients with T1 tumors the *AUC* was 0.60 (95 % *CI* = 0.35–0.86) and in 42 T2 tumors *AUC* was 0.55 (95 % *CI* = 0.38–0.73).

Discussion

Over the past two decades early diagnosis and effective systemic adjuvant therapy has led to improved survival [17, 18] after breast cancer treatment and researchers have now focused on improving the quality of life in long term survivors. More conservative approach has been adopted in breast cancer surgery over this period with breast conservation surgery (BCS) and sentinel node biopsy replacing mastectomy and axillary clearance in eligible patients, offering them a better

Table 1 Association of clinicopathological variables with non-sentinel metastasis

Variable (total n)	Non sentinel positive ($n = 20$)	Non-sentinel negative ($n = 44$)	<i>P</i> Value Uni variate analysis	<i>P</i> value Multivariate analysis (OR)
T1 tumors ($n = 22$)	8(36.3 %)	14(63.7 %)	0.523	NS
T2 tumors ($n = 42$)	12(28.6 %)	30(71.4 %)		
Grade			0.293	NS
Low and intermediate ($n = 36$)	12(33.3 %)	24(66.7 %)		
High ($n = 24$)	5(20.8 %)	19(79.2 %)		
Histology			0.087	NS
IDC [$n = 60$]	17 [28.3 %]	43 [71.7 %]		
ILC [$n = 4$]	3 [75 %]	1 [25 %]		
Multifocal			0.094	NS
Yes [$n = 6$]	0	6 [100 %]		
No [$n = 58$]	20 [34.5 %]	38 [65.5 %]		
Lymphovascular invasion			0.530	NS
Yes [$n = 11$]	3 [27 %]	8 [73 %]		
No [$n = 53$]	17 [32 %]	36 [67.9 %]		
Extra-capsular invasion			0.002	0.0001 (11.3)
Yes [$n = 15$]	11 [73.3 %]	4 [26.7 %]		
No [$n = 49$]	9 [18.3 %]	40 [81.7 %]		
ER positive			0.258	NS
Yes [$n = 53$]	18 [33.9 %]	35 [66.1 %]		
No [$n = 11$]	2 [19 %]	9 [81 %]		
Sentinel			0.04	0.99
Only 1 node + [$n = 51$]	13 [25.6 %]	38 [74.5 %]		
>1 node + [$n = 13$]	7 [53.8 %]	6 [46.2 %]		
Size of sentinel mets			0.232	0.99
Micro-mets	0 [0 %]	3 [100 %]		
Macro-mets	20 [32.8 %]	41 [67.2 %]		

Table 2 Comparing original MSKCC prospective group with our study group

Variables	MSKCC <i>n</i> = 373	Our study <i>n</i> = 64	<i>p</i> value
Age			
<50	157(42.1)	28 (43.7)	0.321
>50	216(57.9)	36(56.3)	
Tumor size			
<5 mm	13(3.5)	0(0)	0.0002
5 to 10 mm	49(13.1)	0(0)	
11–20 mm	166(44.5)	22(34.4)	
>20 mm	145(38.5)	42(65.6)	
Grade			
I	11(2.9)	2(3.1)	0.272
II	175(46.9)	34(53.1)	
III	129(34.6)	24(37.5)	
Lobular	58(15.6)	4(6.3)	
LVI			
Yes	154(41.3)	11(17.2)	0.001
No	219 (58.7)	53(82.8)	
Multifocality			
Yes	132 (35.4)	6(9.4)	0.0001
No	241(64.6)	58(90.6)	
ER positive	290(77.7)	53(82.8)	0.362
ER negative	83(22.3)	11(17.2)	
No. of positive SLN			
1 only	265(71)	51(79.7)	0.651
2	75(29)	9(14.1)	
3	21(5.6)	3(4.7)	
4	8(2.1)	1(1.6)	
>5	4(1.1)	0(0)	
No. of negative SLN			
0	132(35.4)	10(15.6)	0.03
1	79(21.2)	18(28.1)	
2	72(19.3)	15(23.4)	
3	41(11)	13(20.3)	
4	22(5.9)	4(6.3)	
>5	27(7.2)	4(6.3)	
≥3 nodes harvested	24.10 %	64.10 %	

quality of life. For the majority of patients with pathologically positive SLNs, completion ALND is recommended by the American Society of Clinical Oncology Guidelines and the National Comprehensive Cancer Network (NCCN) guidelines. However recent ACSOG Z-011 trial demonstrated that patients with limited sentinel node positivity (1–2 SLNs) treated with breast conservation surgery, adjuvant whole breast irradiation and systemic therapy did not benefit from completion ALND [19]. Currently, Z-011 results would have to be applied with great caution to patients undergoing mastectomy

since they may not receive adjuvant radiotherapy as was the case in all Z-011 patients. Breast cancer surgeons are now debating about the requirement of axillary clearance in all sentinel positive cases proposing a more selective approach based on individual risk [20–25].

Authors have identified that tumor and nodal characteristics act together to impact the occurrence of NSLN metastasis. An important tumor characteristic that increases the likelihood of NSLN metastasis is tumor size [26–28]. Joseph et al. [27] observed in his study that incidence of NSLN metastasis in T1a, T1b and T1c tumors were 0, 12 and 42 % respectively. Boler et al. [29] in his study reveals that 30 % of T1 tumors and 45 % of T2 tumors had NSLN involvement. Other tumor characteristics reported to be associated with NSLNM are tumor grade [30, 31] and lymphovascular invasion (LVI) [29–32]. In our study, we could not identify a statistically significant association of tumour size, grade and lymphovascular invasion with non-SLN metastasis which could be due to smaller sample size and fewer subjects having NSLN metastasis (*n* = 20).

Overall size of metastasis in sentinel node is demonstrated to be one of the most significant predictor of residual axillary disease in axilla. In a meta-analysis by Degnim et al. [33], sentinel node metastasis size appeared to be the strongest predictor of non-SLN involvement. Reynold et al. [34] and Chu et al. [35] reported a NSLN involvement rate of 5 % and 6 % respectively, in patients with T1 tumors and SLN micrometastasis. In our study, we identified that patients who had micrometastasis in SLNB (*n* = 3) had no additional nodal involvement in completion ALND. Several centers are now considering omission of ALND in SLN micrometastasis patients as a safe option, given the low rate of additional metastasis in completion ALND. The results of the NSABP B-32 [36] and ACSOG Z0010 [37] trials suggest that SLN micrometastases found only by IHC are clinically insignificant.

The number of positive SLNs and nodal ratio (SLN positive/SLN harvested) are demonstrated to be associated with additional nodal metastasis. ACSOG Z-011 trial has specifically limited cases with 1–2 SLNs positive to SLNB alone group on the basis that this group has lesser risk of residual disease in axilla. Wong et al. [26], Boler et al. [29], Chu et al. [35] found in their respective studies that 50, 51 and 56 % of cases with multiple positive sentinel nodes (>1 SLN+) had NSLN involvement as compared to 32, 30 and 31 % of patients with 1 SLN+. In our study, 53.8 % of patients with more than one sentinel node positive had NSLN involvement as compared to 25.3 % in patients with single positive SLN. Multiple SLNs positivity had a significant association (*p* = 0.04) with NSLN involvement in univariate analysis. Also 41.9 % of individuals with nodal ratio ≥ 0.5 had NSLN involvement as against 21.3 % in nodal ratio < 0.5 (though not statistically significant). *In summary our study a positive*

Fig. 1 Receiver operating characteristic curve to calculate the discriminatory accuracy of MSKCC nomogram in predicting NSLN metastasis. AUC = 0.558 (95 % CI = 0.406 to 0.710)

correlation exists between SLN size, no. of positive SLNs and nodal ratio and NSLN metastasis (although statistically significant association was obtained only in multiple SLN positivity).

Extra-capsular invasion (ECI) in sentinel nodes is proved to be one of the strongest predictor of further metastasis in axilla. *ECI of the SLN occurs at vascular root of lymphnode hilum and represents tumor deposits in transit to other sites* [38]. Most studies have observed that 60–70 % of patients with ECI in SLNs have NSLN positivity as compared to 20–30 % in ECI negative cases [29, 30, 39–43]. Similarly in our study 73 % of cases with ECI in SLNs had NSLN metastasis. We also observed *ECI to be independent predictive factor for NSLN metastasis in both univariate and multivariate analysis*.

Based upon the tumor and sentinel nodal characteristics associated with non-SLN metastasis, *MSKCC group developed a nomogram to calculate the risk of NSLN metastasis which could guide the physician and patient on decision making of ALND. It takes into consideration 8 variables for risk assessment and is likely to perform better diluting the differences in patient/tumor characteristics and pathological assessment*. However validation by external groups has only yielded discordant results (Table 3). The probable reasons quoted for discrepancy are differences in age, tumor/sentinel characteristics, heterogeneity in SLNB technique and pathological assessment.

A model performs accurately when the population where it is to be applied is similar to the original cohort where the nomogram was devised. Degnim et al. [33] and Meretoja et al. [40] have demonstrated that performance of a nomogram diminishes when transported from one population to other. Ponzzone et al. [13] observed that compared to their group,

the MSKCC original series had significantly higher proportion of patients with ≥ 3 SLNs removed (24 % vs. 8 %). This could be due to differences in the SLNB concept across these countries. Surgeons in Italy advocate minimum nodes to be excised in SLNB [61] whereas some American surgeons

Table 3 Validation of MSKCC nomogram in literature

Authors, country, year	Sample size	AUC
Coutant et al., France, 2009 [44]	561	0.78
Smidt et al., The Netherlands, 2005 [45]	222	0.77
Lombardi et al. Italy, 2011 [46]	139	0.76
Soni et al., Australia, 2005 [47]	149	0.75
Kuo et al., Taiwan, 2013 [48]	324	0.738
Hidar et al., Tunisia, 2011 [49]	87	0.73
Sasada et al., Japan, 2012 [50]	116	0.73
Alran et al., France, 2007 [12]	588	0.724
Amanti et al., Italy, 2009 [51]	61	0.72
Ponzzone et al., Italy, 2007 [13]	186	0.71
Van la Parra et al., The Netherlands, 2009 [52]	182	0.71
Gur et al., Turkey, 2010 [53]	607	0.705
Poirier et al., Canada, 2008 [54]	209	0.687
Piñero et al., Spain, 2012 [55]	501	0.684
Pal et al., United Kingdom, 2008 [5]	118	0.68
Coufal et al., Czech Republic 2009 [56]	330	0.68
Van der Hoven et al., The Netherlands, 2010 [57]	168	0.68
Sanjuán et al., Spain, 2010 [58]	114	0.67
Moghaddam et al., United Kingdom, 2010 [59]	108	0.63
Fougo et al., Portugal, 2011 [60]	98	0.67
Klar et al., Germany, 2008 [15]	98	0.58

AUC values less than 0.7 are italicized

propose an opposite view [62]. These differences are also likely to be reflected in nomogram results, since higher number of SLNs retrieved could also result in greater number of positive/negative SLNs both of which has strong impact on the nomogram score. Addressing these issues, Klar et al. [15] proposed that standardization of SLNB techniques and pathologic assessment would be desirable but this might be difficult to achieve.

In our validation study the AUC for the entire patient set was 0.58 suggesting poor discriminatory ability. We had greater proportion of patients in T2 category. A subset analysis was done for T1 and T2 tumors separately to ascertain whether the nomogram performed better in T1 tumors. The AUC values were lower than 0.7 (0.55 for T2 and 0.60 for T1) for both groups suggesting poor accuracy.

Besides varied accuracy in different settings, another limitation of nomogram is its poor performance in low risk category. Gábor Cserni [63] elaborated that a test may be accurate in general but can have limited utility in clinically relevant subset. He demonstrated that even in studies which had AUC values >0.7, the observed risk of NSLN metastasis in the low risk group is considerably higher than estimated risk (Table 4). For example in study by Degnim et al. [66] from Mayo clinic, estimated risk of patients with 0–10 % score was 6 % which means that 6 out of 100 patients with a score of 0–10 % by nomogram might have additional nodal metastasis. But in reality 14 % had additional nodal disease. Furthermore it implies that 14 % of patients would have NSLN metastasis if axillary dissection is omitted based on cut-off of 10 % score. In summary, the low probability sub-group indeed has high false negative rates, which could result in under treatment in these patients defeating the very purpose of nomogram. In our study the entire cohort had scores ranging from 20 to 75 % and thus we could not predict the false negative rates with a cut-off of 10 %.

SLN micrometastasis is another low risk factor for NSLNM but several reports indicate poor accuracy of MSKCC nomogram in this subgroup. Several groups [12, 67, 68] have demonstrated poor predictability of MSKCC

nomogram in SLN micrometastasis. This is probably because MSKCC nomogram does not include size of SLN metastasis in its calculation [12]. Van zee et al. admits that volume of metastasis in SLN would be an accurate marker but its measurement can be time consuming and impractical. The authors have used method of detection as a surrogate for SLN size of metastasis in concurrence with previous reports indicating that method of detection correlated with the nodal burden in sentinel nodes [69, 70].

All the above studies indicate that a select sub-set of patients with favorable tumor characteristics (no adverse pathologic features like ECI, LVI, and multiple SLN positivity) have a low probability of residual disease in axilla. Though MSKCC nomogram proved to be accurate in several centers, it could not reliably predict the involvement of NSLN in our study group. Risk factor identified in our study group (ECI) is not a part of MSKCC nomogram which could be the reason for poor performance in our cohort. Similar to our study, an Italian study group [3] identified ECI and SLN macro metastasis to be significant risk factors for NSLNM. They developed a modified prediction tool incorporating these factors into MSKCC nomogram and found it to be with improved specificity.

The usefulness of nomogram should also be seen in the light of results from the AMAROS [71] and ACSOG- Z11 [19] trials which demonstrated that in select subset of sentinel node positive patients, SLNB alone or axillary radiotherapy provide excellent and comparable axillary control as ALND but with reduced arm morbidity. These studies could be practice changing with regard to the need for axillary surgery in node positive women. Until such time where ALND omission becomes a standard of care, these nomograms might serve as useful adjunct to identify risk of NSLNM and individualize the treatment based on the risk category. More data is required to identify risk factors associated with NSLNM in Indian patients and future studies can also modify the existing tools by incorporating the risk factors identified in our population. Lastly our study is limited by sample size and retrospective validation of nomogram. Prospective validation in consecutive patients is desired to ascertain the accuracy of a nomogram.

Table 4 Studies showing underestimation of NSLN metastasis in low-risk category

Study (number of SLN+)	AUC	Low-risk decile	Estimated risk in low risk decile	Observed risk in low risk decile
Kocis L et al. (140) [64]	0.73	0–8 %	6 %	14 %
Smidt ML et al. [45]	0.77	NA	10 %	20 %
Soni NK et al. [65]	0.75	0–10 %	10 %	16 %
Degnim AC Mayo (462) [66]	0.72	0–10 %	10 %	14 %
Degnim AC Michigan (69) [66]	0.86	0–10 %	10 %	11 %
Cripe MH (92) [11]	0.82	0–13 %	9 %	11 %

Conclusions

In our study, sentinel nodes are the only nodes to be involved by tumor in 70 % of the patients. Our findings indicate that multiple sentinel node positivity and extra-capsular invasion in sentinel node significantly predicted the likelihood of additional nodal metastasis. MSKCC nomogram did not reliably predict the involvement of additional nodal metastasis in our study group. Further studies with large sample size can identify risk factors associated with NSLNM in Indian patients and can validate other prediction tools for NSLN involvement to find the most appropriate one for our population.

Compliance with Ethical Standards

Sources of Funding The authors declare no sources of funding.

Conflict of Interest The authors declare no potential conflicts of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Ethical Approval For this type of study formal ethical clearance is not required.

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