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Factors Influencing Non-sentinel Node Metastasis in Patients with Macrometastatic Sentinel Lymph Node Involvement and Validation of Three Commonly Used Nomograms

Hikmet Erhan Güven, Lütfi Doğan, Mahmut Onur Kültüroğlu, Mehmet Ali Gülçelik, Cihangir Özaslan
Department of General Surgery, Ankara Oncology Training and Research Hospital, Ankara, Turkey

ABSTRACT

Objective: Omitting axillary lymph node dissection (ALND) in a subgroup of patients with sentinel lymph node (SLN) metastasis is becoming a widely accepted practice. Avoiding the well-known complications of ALND is the sole aim without compromising the curative intention of surgery.

Materials and methods: The data were probed for breast cancer patients that were operated on between February 2014 and June 2016. SLN biopsies were performed in 507 patients and out of 157 patients who underwent ALND for a metastatic SLN, 151 were found eligible for the analyses as having macrometastatic (>2mm) SLN. MD Anderson, Memorial Sloan Kettering Cancer Center and Helsinki nomograms were also tested in our patient population.

Results: Pathologic tumor size greater than 2 cm, the ratio of metastatic SLN to dissected SLN, metastatic tumor greater than 1 cm and tumors that extended outside the SLN's capsule were found to be associated with non-sentinel node metastasis in both univariate and multivariate tests. MD Anderson nomogram performed well with an area under the curve (AUC) value of 0.72.

Conclusion: Our results suggest that ALND should be considered in patients with macrometastatic SLN greater than 10 mm in size, have extracapsular extension, have metastatic SLNs at a rate of more than 50% and whose primary tumor is greater than 2 cm.

Keywords: Breast cancer, sentinel node, non-sentinel node metastasis, nomogram

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Introduction

Although the latest National Comprehensive Cancer Network (NCCN) guidelines are consistent with American College of Surgeons Oncology Group (ACOSOG) - Z0011 trial with regard to omitting axillary lymph node dissection (ALND) in some patients with metastatic sentinel lymph node (SLN), most surgeons still prefer a complete ALND when SLN is found to be positive (1). However, great inspiration by the study mentioned above has led to detailed investigations regarding the dilemma of avoiding ALND even when SLN is positive for tumor metastasis. Some surgical oncology centers conducted prospective studies or revisited their results and tried to apply some well-known nomograms to their patient population and attempted to perfect the current nomograms to safely discard ALND (2-5).

Since ALND is now considered as a staging procedure for breast cancer that bears clinically substantial risks for known morbidities such as restrictions in shoulder joint motions, seroma formation in the armpit, numbness, lymphedema, it becomes a rather invasive intervention for its purpose (6-8). Regarding local control, axillary radiotherapy has shown promise for comparable outcomes with much lower morbidity rates in T_{1-2} tumors (3). Besides, with the knowledge of ALND providing no more useful information on the stage of the disease in about 30-60% of patients, effective strategies should be developed to avoid it when feasible (9-11).

On the grounds of these data, we conducted retrospective analyses of our patients that were found to have positive SLN and underwent consequent ALND. Characteristics of patients, as well as tumors, were interpreted in a manner to lead the way to decide whether to avoid ALND in a subgroup of patients is applicable and three most common used nomograms were checked in our patient population to

Address for Correspondence :
Hikmet Erhan Güven , e-mail: drerhanguven@gmail.com

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observe their feasibility.

Materials and Methods

The data were probed for breast cancer patients that were operated on between February 2014 and June 2016. SLN biopsies were performed in 507 patients and out of 157 patients who underwent ALND for a metastatic SLN, 151 were found eligible for the analyses as having macrometastatic (>2mm) SLN. None were subjected to any neoadjuvant treatments. SLNs were identified using both Tc-labeled radioactive tracer (nanocolloid) and blue dye (1% methylene blue) that were injected to the site of primary tumor. Radioactivity was detected with a portable gamma probe. The node was defined as sentinel when it was dyed in blue, showed the highest level of radioactivity with regards to adjacent ones or when palpated intraoperatively. When multiple lymph nodes met the above criteria, they were all collected for frozen section examination. Dissected SLNs were studied with frozen section; when found to be positive, ALND was performed in the same session. ALND consisted of the dissection of level I and II axillary nodes. When suspicious nodes were located, they were also included in the specimen regardless of their location. Routine hematoxylin and eosin examination were performed for both ALND and SLN materials postoperatively. Estrogen (ER), progesterone (PR) receptors as well as the Ki-67 and c-erbB-2 status of the tumor was noted. Silver in situ hybridization (SISH) was used to confirm c-erbB-2 status when necessary. Lymphovascular invasion (LVI) in the primary tumor, the size of the metastasis in SLN and presence of extracapsular involvement in the sentinel node(s) were also recorded. ER and/or PR (+), c-erbB-2(-) tumors are defined as Luminal A, whereas ER and/or PR(+), c-erbB-2(+) or c-erbB-2(-) but Ki-6 >15% tumors are considered as Luminal B, and both ER and PR are (-) but c-erbB-2(+) are defined as nonluminal HER2/neu over-expression, and all ER, PR and c-erbB-2(-) tumors are considered as triple negative.

MD Anderson's Breast Cancer Nomogram to Predict Additional Positive Non-SLN without Neoadjuvant Chemotherapy (available online at http://www3.mdanderson.org/app/medcalc/bc_nomogram2/index.cfm?pagename=nsln), Memorial Sloan-Kettering Cancer Center's (MSKCC) Breast Cancer Nomogram: Breast Additional Non SLN Metastases (available online at http://nomograms.mskcc.org/breast/BreastAdditionalNonSLNMetastasesPage.aspx) and Helsinki University Hospital's risk prediction of non-sentinel node metastases after tumor-positive sentinel node biopsy (available for download at http://www.hus.fi/sairaanhoito/sairaanhoitopalvelut/rintarauhaskirurgia/predictive-tools/sivut/default.aspx?redirected=1) nomograms were used to predict non-sentinel lymph node metastasis in our patient population.

Institutional Review Board approval of Ankara Oncology Training and Research Hospital was granted (2016/114).

This study was performed in compliance with the Declaration of Helsinki.

For this type of study, formal patient consent is not required.

This article does not contain any studies with human participants or animals performed by any of the authors.

Statistical Analyses

Statistical analyses were done using the Statistical Package Program software (SPSS®) version 22 (IBM Corp.; Armonk, NY, USA). Categorical data was presented in percentage and comparison between them was done with the Chi-square test. Multivariate analysis was done with logistic regression to predict the independent factors affecting non-sentinel lymph node metastasis. A significant difference was considered when p-value was found to be ≤0.05. Predictive values of three nomograms were checked for calculating the area under curve (AUC) of the receiver operator characteristic (ROC) curve.

Results

Surgical intervention targeting breast lesion was mastectomy in 80 (53%), conventional breast conserving surgery in 27 (18%) and excision with oncoplastic reconstruction (such as inferior and superior pedicle mammoplasties, etc.) in 44 (29%) of patients. Mean size of primary tumors was 27.9 mm, ranging from 6 mm to 70. Upon pathologic examination, 142 (94%) of tumors were infiltrating ductal carcinoma, 4 (2.6%) were in purely lobular type and 5 (3.3%) were mixed or other pathologic types. Tumors were mostly located in the outer upper quadrant of the breast (n=105, 69.5%). Multifocal tumors were detected in 26 patients (17.2%). Other characteristics of 151 patients and tumors are summarized in Table 1.

Table 1. Patient and tumor characteristics

Patient and Tumor Characteristics		n (%)
Age	<50	58 (38.4)
	≥50	93 (61.6)
Pathologic Tumor Size	T1	38 (25.2)
	T2	105 (69.5)
	T3	8 (5.3)
Tumor		
Grade	I	8 (5.3)
	II	67 (44.4)
	III	76 (50.3)
ER	Positive	124 (82.1)
	Negative	27 (17.9)
PR	Positive	121 (80.1)
	Negative	30 (19.9)
C-erb-B2	Positive	46 (30.5)
	Negative	105 (69.5)
Molecular subtype	Luminal A	25 (16.6)
	Luminal B	104 (68.9)
	Triple (-)	15 (9.9)
	Her2 - overexp.	7 (4.6)
LVI	Present	56 (37.1)
	Absent	95 (62.9)
Extracapsular Extension	Present	108 (71.5)
	Absent	43 (28.5)

ER: Estrogen Receptor; PR: Progesterone Receptor; LVI: Lymphovascular Invasion

The size of metastatic sentinel lymph nodes ranged between 3-40mm (mean 12.6mm) and all had macrometastatic disease (>2mm). Descriptive statistics regarding axillary lymph nodes are given in Table 2.

Among many variables tested, four of them showed statistical significance: pathologic tumor size greater than 2cm, the ratio of metastatic SLN to dissected SLN, metastatic tumor greater than 1 cm and tumors extending outside the SLN capsule. Univariate analyses of variables are summarized in Table 3.

All factors mentioned above that affect the non-sentinel lymph node involvement kept their significance on multivariate analysis. The multivariate analysis to analyze the independent factors associated with non-sentinel lymph node involvement is shown in Table 4.

The AUC values for MD Anderson, Helsinki and MSKCC nomograms were 0.72, 0.65, and 0.64, respectively (Figure 1).

Discussion and Conclusion

With the knowledge of axillary dissection's complicative nature, efforts are concentrated on avoiding it when applicable. Accurate prediction of metastases to axilla beyond sentinel node(s) is the focus of interest regarding the prevention of unnecessary ALND. This gained more importance with reports stating that 40-70% of patients with positive SLN have further metastasis in the remaining axilla, making ALND superfluous in almost half of them (9-11). Non-sentinel lymph node metastasis was absent in 60 of our patients (39.7%) placing them in the unnecessarily performed ALND group.

The age of the patient, pathologic tumor size, grade, histology, multifocality, hormone receptor status, Ki-67 and c-erbB-2 expression and LVI are found to be related to non-sentinel node metastasis in previous studies (12-16). Among those tumor-related parameters, only tumor size is found to be associated with non-sentinel node involvement in our series.

The number of sentinel lymph nodes dissected and the ratio of metastatic/dissected sentinel nodes, tumor burden in metastatic sentinel node and extracapsular invasion to the surrounding tissue were investigated using both univariant and multivariant analyses and found related with non-sentinel lymph node involvement in various studies (17-22). Considering our findings, it can be stated that when more than half of the dissected sentinel nodes are infiltrated, the likelihood of having metastasis in the rest of the axillary lymph nodes significantly increases. Metastatic SLN greater than 10 mm in size is found to pose a risk for non-sentinel node involvement according to our findings. Furthermore, the strongest correlation was found between extracapsular extension of the tumor in the SLN with a hazard ratio of 13.8 (Table 4).

Table 2: Descriptive statistics of axillary lymph nodes

	Minimum	Maximum	Median
Dissected SLN (n)	1	9	2
Metastatic SLN (n)	1	7	1
Metastatic SLN size (mm)	3	40	11
Ratio of metastatic/ dissected SLNs (%)	11	100	60
Dissected ALN1 (n)	7	45	19
Metastatic ALN1 (n)	0	36	1

SLN: sentinel lymph node; ALN: axillary lymph node

Table 3: Univariate analysis of the data

Variable	p (2-sided)
Age <50 vs. ≥50	0.124
Pathologic tumor size ≤2cm vs. >2cm	0.014
Pathologic tumor size T1-T2-T3	0.235
Histopathology of the tumor IDC, ILC, mixed and other	0.692
Grade I-II-III	0.986
ER positive vs. negative	0.167
PR positive vs. negative	0.157
c-erb-B2 positive vs. negative	0.391
Ki-67 <15 vs. ≥15	0.271
LVI Present vs. absent	0.086
Multifocality Present vs. absent	0.534
Ratio of metastatic/dissected SLN's ≤50% vs. >50%	0.005
Metastatic SLN size <10mm vs. ≥10mm	0.002
Extracapsular extension Present vs. absent	0.0001

ER: estrogen receptor; PR: progesterone receptor; LVI: lymphovascular invasion

Table 4: Multivariate analysis of factors affecting non-sentinel node metastasis

		95% Confidence Interval		Odds
Variable	p	lower	upper	Ratio
Tumor Size ≤2cm vs. >2cm	0.043	1.018	5.626	5.2
Ratio of metastatic/ dissected SLN's ≤50% vs. >50%	0.038	1.037	4.521	7.4
Metastatic SLN size <10mm vs. ≥10mm	0.045	1.014	4.910	5.6
Extracapsular extension Present vs. absent	0.005	1.372	9.458	13.8

SLN: sentinel lymph node

Öz et al. (25) reported that Ki-67 and c-erb-B2 expression is connected with non-sentinel metastasis and also two other studies stated c-erb-B2 as an independent factor (23, 24). We found no direct relation between Ki-67, c-erb-B2, hormone receptor status and non-sentinel involvement. Molecular subtypes are thought to influence the spread of the disease regionally. Zhou et al. (26) reported that both luminal A and B subtypes were riskier in terms of non-sentinel node metastasis. Gülben et al. (27) also found luminal B subtype was associated with non-sentinel node involvement. However, both studies grouped tumors considering the Ki-67 expression rate. We categorized tumors according to their Ki-67 expression rate and found no relation regarding non-sentinel node metastasis.

Some of the aforementioned factors were used in combination to constitute nomograms like MD Anderson, MSKCC, and Helsinki (21, 28, 29). These three nomograms are widely used in research studies and readily accessible. When the MD Anderson, MSKCC, and Helsinki nomograms were applied, only the MD Anderson nomogram passed the generally accepted threshold for discrimination with an AUC value of 0.72. Helsinki and MSKCC nomograms also did well, but were not powerful enough for our patient population with AUC values of 0.65 and 0.64 respectively.

For patients who do not meet the criteria stated in ACOSOG Z0011 trial, nomograms sound handy in deciding whether to proceed with ALND or not. We tried the three most commonly used, readily available, online and easy-to-use nomograms in our patient population with macrometastatic SLN involvement. Only the MSKCC nomogram did well just above the minimal limit of significance. With our 60% positivity rate on the remaining axilla, it seems far from convenient for us to rely on. However, removing a mean number of 19.6 lymph nodes for clearing a mean number of only 3 metastatic nodes is not acceptable, either. More efforts should be made to rationalize the predictive power of nomograms for non-sentinel node metastasis, especially at the presence of macrometastatic SLN. The more variables are taken into account, the more powerful a nomogram may become.

Until alternative therapies are proven to be as effective as ALND, for patients that do not meet the criteria of ACOSOG Z0011, we prefer to complete the dissection of axilla when faced with metastasis in the SLN.

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