

Factors Predictive of Sentinel Lymph Node Involvement in Primary Breast Cancer

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Abstract. *Background/Aim:* Sentinel lymph node biopsy (SLNB) has replaced axillary lymph node dissection (ALND) for axillary staging in patients with early-stage breast cancer. The need for therapeutic ALND is the subject of ongoing debate especially after the publication of the ACOSOG Z0011 trial. In a retrospective trial with univariate and multivariate analyses, factors predictive of sentinel lymph node involvement should be analyzed in order to define tumor characteristics of breast cancer patients, where SLNB should not be spared to receive important indicators for adjuvant treatment decisions (e.g. thoracic wall irradiation after mastectomy with or without reconstruction). *Patients and Methods:* Between 2006 and 2010, 1,360 patients with primary breast cancer underwent SLNB with/without ALND with evaluation of tumor localization, multicentricity and multifocality, histological subtype, tumor size, grading, lymphovascular invasion (LVI), and estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 status. These characteristics were retrospectively analyzed in univariate and multivariate logistic regression models to define significant predictive factors for sentinel lymph node involvement. The multivariate analysis demonstrated that tumor size and LVI ($p < 0.001$) were independent predictive factors for metastatic sentinel lymph node involvement in patients with early-stage breast cancer. *Conclusion:* Because of the increased risk for metastatic involvement of axillary sentinel nodes in cases with larger breast cancer or diagnosis of LVI, patients with these breast cancer characteristics should not be spared from SLNB in a

clinically node-negative situation in order to avoid false-negative results with a high potential for wrong indication of primary breast reconstruction or wrong non-indication of necessary post-mastectomy radiation therapy. The prognostic impact of avoidance of axillary staging with SLNB is analyzed in the ongoing prospective INSEMA trial.

The axillary lymph nodes are the primary site of lymphatic drainage from all areas of the breast. The extent of axillary lymph node involvement in breast cancer has been recognized as the strongest predictor of recurrence and survival, as the extent of lymph node involvement increases, survival decreases regardless of tumor size (1, 2).

Axillary lymph node dissection (ALND) has been an integral part of the surgical management of breast cancer since the description of radical mastectomy by Halstedt in 1894 (3). Although ALND reliably stages the axilla and is an effective method for local control, it is of no benefit to women whose axillary lymph nodes do not contain metastases. This radical surgical method is associated with significant long-term complications, including lymphedema, sensory morbidity and restriction in shoulder functionality (4).

Surgical management of the axilla changed radically with the introduction of the sentinel lymph node biopsy (SLNB) in the early 1990s (5, 6). Patients with node-negative breast cancer can be spared the morbidity of ALND. However, if the sentinel node is found to have metastatic involvement, completion ALND is routinely performed. Metastatic involvement is histologically analyzed with serial sectioning and immunohistochemistry (IHC) staining to identify macrometastases, micrometastases, and isolated tumor cells.

While in the NSABP B32 trial, investigating axillary resection with sentinel node dissection, 16% of the 3,986 patients with SLN-negative disease had micrometastatic involvement of the axillary lymph nodes, 11% of these patients also had isolated tumor cells (pN0i+). Because most of these patients received systemic adjuvant therapy, it is

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Key Words: Breast cancer, sentinel node biopsy, predictive factors, lymph node involvement.

clear that fewer than 1% of patients would have experienced a survival benefit from routine ALND (7).

Despite all the evidence supporting the need for ALND in patients with macrometastatic involvement of a SLN, The American College of Surgical Oncology Group (ACOSOG) Z0011 trial was performed to examine the role of ALND in clinically node-negative patients found to have macrometastatic involvement of one or two SLNs. All patients underwent treatment with lumpectomy, radiation therapy, and adjuvant systemic therapy. At a median of 6.3 years of follow-up, there were no significant differences between the sentinel lymph node-only and the ALND groups in the rates of overall locoregional recurrence. The 5-year survival rates for patients without and with IHC-detected metastases did not differ significantly (95.8% vs. 95.1%; $p=0.53$) (8). Additionally, neither disease-free nor overall survival differed significantly between groups. As a clinical consequence, ALND is no longer recommended when there is macrometastatic involvement of one or two SLNs (clinically node-negative) and patients fulfil the eligibility criteria of the ACOSOG Z0011 trial (9).

More recently, it has been recognized that breast cancer is not a uniform disease but a group of different molecular intrinsic subtypes with differing prognoses (10). Between these subtypes, the incidence of lymph node metastasis differs (11). Several predictors of lymph node metastasis have been described such as multifocality, higher histological grade, lateral and retroareolar location of the tumor, larger tumor size and the presence of lymphovascular invasion (LVI) (12). The predictive role of estrogen receptor (ER) and progesterone receptor (PR) expression and human epidermal growth factor receptor 2 (HER2) status, histological subtype and age remains controversial (13-16).

The goal of our study was to determine prognostic and predictive factors associated with SLN metastases in patients with primary breast cancer in order to derive future evidence to define a clinically node-negative patient subgroup where SLNB might not be recommended.

Patients and Methods

Patients. Data were obtained from the database of the Breast Center of the Department of Gynecology and Obstetrics, University Medical Center of Cologne, Germany. Between October 2006 and December 2010, 1,360 patients with primary invasive breast cancer (cT1-cT3) underwent resection of the primary tumor and axillary staging by SLNB. An ALND was performed if required by gold standard. The local treatment consisted of wide excision followed by adjuvant whole-breast radiotherapy or mastectomy with or without radiotherapy (according to national guidelines). Patients treated for local recurrence, with carcinoma *in situ* only, who received neo-adjuvant therapy were diagnosed with primary metastatic disease were excluded.

Predictive factors. In order to determine factors associated with metastatic involvement of SLNs, each of the following parameters were evaluated: age at diagnosis, histological subtype, tumor size, histological

Table I. *Clinical and pathological characteristics of analyzed patients (n=1,360).*

Characteristic	Value
Age	
Range (years)	23-89
Mean (years)	57.0
Number of foci, n (%)	
Unifocal	1256 (91.8)
Multifocal	113 (8.2)
Histological grade, n (%)	
1	39 (2.8)
2	985 (72.0)
3	311 (22.7)
Unknown	34 (2.5)
Tumor location, n (%)	
Upper outer	941 (68.7)
Upper inner	167 (12.2)
Lower outer	122 (8.9)
Lower inner	79 (5.8)
Central	30 (2.2)
Overlapping	15 (1.1)
Unknown	7 (1.1)
Histological subtype, n (%)	
Invasive ductal/DCIS	1015 (74.1)
Invasive lobular	162 (11.8)
Invasive ductal and lobular	24 (1.8)
Other	149 (10.9)
Unknown	19 (1.4)
Axillary lymph node dissection, n (%)	
No	1079 (78.8)
Yes	281 (20.5)
Unknown	9 (0.7)
Tumor size, n (%)	
T1a/b	285 (20.8)
T1c	561 (41.0)
T2	372 (27.2)
T3	41 (3.0)
Unknown	110 (8.0)
Nodal status, n (%)	
pN0	1079
pN1	240 (78.8)
pN2-3	48 (3.5)
Unknown	2 (0.2)
ER status, n (%)	
Positive	1145 (83.6)
Negative	206 (15.0)
Unknown	18 (1.4)
PR status, n (%)	
Positive	1068 (78.0)
Negative	283 (20.7)
Unknown	18 (1.3)
HER2 status, n (%)	
Positive	147 (10.7)
Negative	1175 (85.8)
Unknown	47 (3.5)
LVI, n (%)	
Positive	271 (19.8)
Negative	1027 (75.0)
Unknown	71 (5.2)

DCIS: Ductal carcinoma *in situ*; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; LVI: lymphovascular invasion; PR: progesterone receptor.

Table II. Univariate analysis of characteristics.

Variable	Comparison	Odds ratio (95% CI)	p-Value
Age	Per decade	0.93 (0.83-1.04)	0.210
Number of foci	Unit increase	1.61 (1.06-2.48)	0.027
Histological grade	1 vs. 2	1.44 (0.89-2.33)	0.143
	1 vs. 3	1.61 (0.93-2.72)	0.07
	2 vs. 3	1.12 (0.83-1.53)	0.46
Tumor location	Upper outer vs. central	2.08 (0.97-4.40)	0.059
	Upper outer vs. upper inner	0.69 (0.45-1.08)	0.012
	upper outer vs. lower inner	0.77 (0.43-1.41)	0.399
	upper outer vs. lower outer	0.93 (0.58-1.48)	0.744
	Upper outer vs. overlapping and retroareolar	2.11 (1.13-3.95)	0.019
Tumor size	T1	2.80 (2.11-3.72)	0.001
	T2	5.23 (2.76-9.93)	0.001
	T3	10.89 (0.99-122.0)	0.51
LVI	Ductal vs. lobular	1.125 (0.76-1.65)	0.549
	Ductal vs. other	0.378 (0.23-0.62)	0.001
LVI	Present vs. absent	3.62 (2.54-5.13)	0.001
ER status	Positive vs. negative	1.187 (0.815-1.73)	0.372
PR status	Positive vs. negative	1.125 (0.812-1.56)	0.478
HER2 status	Positive vs. negative	1.32 (0.89-1.95)	0.161

ER: Estrogen receptor; HER2: human epidermal growth factor receptor 2; LVI: lymphovascular invasion; PR: progesterone receptor.

nuclear tumor grade, number of SLNs removed, IHC of ER and PR, HER2 status, LVI, the number of patients receiving only SLNB, or ALND following SLNB. Univariate and multivariate analyses were performed. Factors significantly associated with metastatic involvement of SLN in univariate analysis were included in the multivariate model.

SLN detection. The SLNs were preoperatively marked by injecting a radioactive isotope (^{99m}Tc-labelled nanocolloid) into Sappey's subareolar plexus (17). The SLNs were identified with a hand-held gamma detector (Neoprobe®; Ethicon Endosurgery, Cincinnati, OH, USA) before surgical removal.

Histological examination of SLNs. SLNs were routinely examined by serial sectioning. Every 200 µm, two sections were stained, one with routine hematoxylin and eosin (H&E) and one by IHC using cytokeratin. Lymph nodes in ALND specimens were examined by H&E staining using three sections per node. According to gold standard, lymph nodes from lobular breast cancer classified as lymph node-negative on H&E were additionally stained for IHC examination of E-cadherin.

Statistical methodology. To analyze the effect of various predictors on the presence or absence of positive ALNs, logistic regression models were used. Univariate analysis was performed for a number of predictors of which a relationship to lymph node involvement was to be expected. Thereafter, a multivariate analysis was performed including those predictors that were shown to be related in the univariate analysis. Odds ratios and p-values were calculated. The 95% confidence intervals (CI) were calculated and pair-wise comparison between groups was made to determine which results were statistically significant. All p-values smaller than 0.05 were used for statistical significance. All analyses were performed using SPSS software version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Between October 2006 and December 2010, SLNB was performed in 1,360 patients with unilateral breast cancer, and in 38 patients with bilateral breast cancer.

Table I shows the clinical and pathological characteristics of the patients. The mean age was 57 years (range=23-89 years). Of the patients who underwent SLNB, 281 patients (20.5%) were lymph node-positive and underwent ALND according to gold standard at the time (18). A total of 846 (61.8%) had a T1 tumor size, 1,145 (83.6%) patients were ER-positive, while 147 (10.7%) of the patients had HER2-positive breast cancer. LVI was histologically detected in 271 (19.8%) patients. For patients whose characteristics were not present in records, these data were summarized as unknown.

Results of the univariate analyses are presented in Table II. There was a significant association of number of tumor foci with ALN involvement (OR=1.61, 95% CI=1.06-2.48; p=0.027). There was an overall effect of tumor grade, the higher the tumor grade, the higher the probability of ALN metastasis.

Patients with grade 2 tumors were found to have a lower probability of ALN metastasis compared to patients with grade 3 tumors (OR=1.12, 95% CI=0.83-1.53; p=0.46) and patients with grade 1 tumors had the lowest probability of ALN metastasis (grade 1 vs. grade 3: OR=1.61, CI=0.93-2.72; p=0.07), without statistical significance.

The tumor location was also found to have a statistically significant effect on nodal involvement. Patients with tumors

of the upper outer quadrant had a higher probability of positive ALNs compared to patients with tumors of the upper inner quadrant (OR=0.69, 95% CI=0.45-1.08; $p=0.012$). However, patients with a retroareolar tumor localization had a higher probability of positive ALNs (OR=2.11, 95% CI=1.13-3.95; $p=0.019$).

According to tumor size, the risk for ALN metastasis steadily increased from the smallest to the largest tumors (OR=5.23, 95% CI=2.76-9.93; $p<0.001$) Furthermore, there was a highly significant effect of LVI. Patients with LVI had a much higher probability of positive ALNs compared to patients without LVI (OR=3.62, 95% CI=2.54-5.13; $p<0.001$).

Subsequently, multivariate analysis was carried out on those variables found to be statistically significant in univariate analyses to analyze for significant independence as predictive markers for ALN involvement. Moreover, histological subtype was included as we found the histological subtype to be a predictive factor for lymph node involvement (Table II). The results of multivariate analysis are presented in Table III.

LVI and tumor size were found to be the most powerful predictors of nodal status ($p<0.001$). All other variables (tumor localization, histological subtype) of the univariate analyses were found not to be independently significant in the multivariate analyses.

Discussion

Since the introduction of SLNB as a staging procedure for the ALN status, the role of ALND has decreased worldwide (17). Today, SLNB is a well-established procedure for axillary staging, with a false-negative rate lower than 5%, as well as its higher pathological accuracy for the detection of occult lymph node metastases in the SLN (micrometastasis, isolated tumor cells) (19-21). The therapeutic benefit of ALND is much more controversially discussed. In the NSABP-B04 study, ALND was not able to improve overall survival in patients with breast cancer, underlining that breast cancer is a systemic disease from its onset such that removing involved or uninvolved ALNs is unlikely to affect survival (22). On the other hand, a meta-analysis of the Early Breast Cancer Trialists' and Collaborative Group demonstrated that improved locoregional control in patients with early-stage breast cancer translated into a survival benefit after 15-year follow-up (23).

The results of the ACOSOG Z0011 trial suggest that ALND should be avoided in patients with 1-2 macrometastatically involved SLNs who are treated with breast-conserving surgery, whole-breast irradiation and adjuvant systemic therapy (9). Moreover, the debate on the role of therapeutic ALND is still ongoing because of some limitations of that trial regarding the completeness of accrual, adherence to the scheduled surgical treatment and the applied radiotherapy (24). In recent years, several mathematical models (nomograms)

Table III. *Multivariate analysis of characteristics.*

Variable	<i>p</i> -Value
Tumor location	0.602
Tumor size	0.0001
Histological type	0.243
Lymphovascular invasion	0.0001

have been developed which can be used to predict lymph node involvement based on SLNB results. These nomograms are based on tumor-related characteristics such as tumor subtype, size, LVI, grading, and hormone receptor status (25). However, these nomograms lack sufficient accuracy and have limited clinical practicability. As a matter of fact, in the ACOSOG Z0011 trial, more than 25% of patients in the SLN-only arm had involved axillary non-SLNs left without a negative effect on disease-free or overall survival.

For future clinical practice, the question arises as to whether a subgroup of patients with a low risk for SLN metastases can be defined for whom SLNB can be avoided altogether. This question is being prospectively analyzed in the ongoing INSEMA-trial (NCT02466737). In this trial, in the first part, patients with clinically node-negative early-stage breast cancer are randomized at a one-to-four ratio to no SLNB and SLNB. In the second part, if 1-2 SLNs are found to be involved, patients are randomized to no ALND and ALND (according to the ACOSOG Z0011 protocol).

The status of the axilla is increasingly important for primary reconstruction in order to avoid radiotherapy of the thoracic wall. Furthermore, the risk of LN involvement may influence the timing of breast reconstruction. In patients at low risk of LN involvement, primary reconstruction after mastectomy can be considered, while in patients at high risk of LN involvement, a second procedure in favor of autologous reconstruction may be preferred. In clinical practice, in order to exclude the necessity for post-mastectomy radiation therapy when primary implant reconstruction is planned, we recommend pre-therapeutic SLNB. The detection of metastatic involvement of a SLN is an indication for post-mastectomy radiation therapy and a relative contraindication for primary implant reconstruction because of an increased incidence of capsular fibrosis (26).

In our analysis, the presence of LN metastasis in 1,360 patients with breast cancer (21.9%) is not in accordance with the incidence range reported in literature (33.2-39%). Three parameters emerged as dependent predictors of the ALN status in univariate analyses, namely the number of foci, tumor location, primary tumor size and LVI. The age of the patient at diagnosis and histological grade did not retain significance in univariate analyses. These results are largely in concordance with other series published in the literature (27, 28).

LVI has been described as the strongest independent predictor of nodal involvement (29). This finding was confirmed in the present study. Of our patients with LVI, 75.0% had positive ALNs. In our series, tumor size was the second strongest dependent predictive factor. Tumor size has also been shown to be an independent factor in various studies (30,31). For example, in patients with tumors smaller than 10 mm, 15.4% were found to be lymph node-positive after SLNB, while 33.8% of patients with tumor sizes between 20 mm and 50 mm were so.

Our results will not alter the indications for SLNB. Even patients with a high probability of LN involvement are candidates for SLNB as a subgroup of these patients can safely avoid an ALND.

Finally, this study cannot be used to predict the tumor load in the axilla. There is an ongoing debate on the prognostic implications of minimal LN involvement. With the introduction of SLNB, there was an upstaging of a subgroup of patients. These patients have mainly isolated tumor cells or micrometastasis in the SLN due to a more detailed histological examination. However, our model for predicting ALN involvement cannot differentiate between micro- or macrometastatic disease in the axilla (data not shown). LVI and tumor size emerged as the most powerful independent predictors of ALN metastasis, followed by the location of the tumor in the breast and the histological subtype.

These results can be used for decision making in clinical practice and should be further prospectively analyzed in the ongoing INSEMA trial. The information regarding involved SLNs is important to indicate the need for postoperative radiotherapy of the thoracic wall after mastectomy with or without primary reconstruction of the breast. The avoidance of SLNB in all patients with early-stage breast cancer can negatively affect the prognosis of some patients, when postoperative radiation therapy necessary after mastectomy (including skin- or nipple-sparing mastectomy with reconstruction) cannot be indicated.

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Received March 13, 2018

Revised April 29, 2018

Accepted May 3, 2018