The Breast 21 (2012) 518–523

Contents lists available at SciVerse ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Factors predicting the non-sentinel lymph node involvement in breast cancer patients with sentinel lymph node metastases

D.E. Boler [a], C. Uras [a], U. Ince [b], N. Cabioglu [a,*]

[a] Department of Surgery, Faculty of Medicine, Acibadem University, Istanbul, Turkey
[b] Department of Pathology, Faculty of Medicine, Acibadem University, Istanbul, Turkey

ARTICLE INFO

Article history:
Received 12 September 2011
Received in revised form
2 February 2012
Accepted 19 February 2012

Keywords:
Non-sentinel lymph node metastases
Isolated tumor cells
Micrometastasis
Breast cancer
Sentinel lymph node metastasis
Luminal A
Luminal B
HER2
Triple negative
Extracapsular invasion

ABSTRACT

Objective: In a significant proportion of patients, the sentinel lymph node (SLN) is the only involved axillary node. The goal of the present study was to identify predictive factors associated with a positive SLN and with a positive non-SLN in patients in whom axillary lymph node dissection (ALND) was performed.

Methods: Data was reviewed for patients with T1–2 invasive breast cancer who underwent SLN biopsy with or without axillary dissection in a single institution between July 2000 and May 2010. The SLNs were examined by serial sectioning and H&E staining, and by cytokeratin immunostaining in suspicious cases.

Results: Of 332 patients with SLNB, 134 had SLN positivity, and 116 of them further underwent completion axillary dissection. Patients with T2 tumors (OR = 3.2; 95% CI, 1.74–5.58), or tumors with lymphovascular invasion (OR = 8.0; 95% CI, 4.44–14.27), or invasive ductal cancer (OR = 2.92; 95% CI, 1.1–8.0) were more likely to have a positive SLN. In patients with ALND, the non-SLN involvement rates were 10%, 11.5% and 50% in patients with isolated tumor cells (ITC), micrometastasis and macrometastasis, respectively. Finding of ITC or micrometastasis in SLNs (OR = 0.28; 95% CI, 0.08–0.99) or presence of extracapsular invasion (ECI) in SLN (OR = 0.24; 95% CI, 0.09–0.67) were the predictive factors of not having a non-SLN metastasis in logistic regression analysis.

Conclusions: These findings suggest further axillary surgery can be best omitted in patients with micrometastasis while validation of nomograms including factors such as ECI are still needed to be studied in patients with macrometastasis.

Introduction

Sentinel lymph node biopsy (SLNB) has been widely used to spare women from morbidities of axillary dissection in breast cancer. Recent randomized trials[1–4] have shown similar outcome in patients with axillary lymph node dissection and SLNB alone when the SLNB was found to be negative. When the SLNs are positive for metastatic disease, axillary dissection is the accepted standard care. However, in a considerable number of patients, the non-sentinel nodes are free of disease and the patients are prone to morbidities of axillary dissection without benefit from the procedure.[5,6]

The non-SLN involvement generally ranges from 34% to 50% among patients with SLN positivity[7–11] whereas it has been found to be between 6.5% and 21% in ITC and micrometastatic disease in published series.[11–15] Previous randomized trials including The NSABP-B04, NSABP B-32 have shown that axillary lymph node dissection (ALND) confers no survival advantage except providing prognostic information in terms of disease staging.[16–18] Axillary recurrence risk is low after removal of SLN alone, even with a predicted false-negative rate of approximately 10%.[5] Additionally, recent reports from randomized prospective trials indicated that systemic chemotherapy and radiotherapy may sterilize the remaining nodes.[2,19–22] These findings have also been recently supported by the Z0011 results and International Breast Cancer Study Group trial 23-01.[6,23,24]

Despite numerous studies[25–42] investigated clinicopathologic factors associated with non-SLN metastases, there is still a gray zone whether a subgroup of patients can be defined in whom axillary dissection can be avoided. Size of the primary tumor, size of SLN metastasis, extracapsular invasion (ECI), lymphovascular invasion (LVI), number of positive SLNs, histologic grade (HG),

* Corresponding author. Acibadem University Faculty of Medicine and Acıbadem Maslak Hospital, Breast Health Clinic, Maslak, Sariyer, Istanbul, Turkey. Tel.: +90 304 4191; fax: +90 286 11 53.
E-mail address: neslicab@yahoo.com (N. Cabioglu).

0960-9776/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.breast.2012.02.012

hormone receptor status, invasion depth in SLN have each been identified as predictors of non-SLN metastases with some degree of inconsistency between studies.[25–42] By using these clinicopathologic factors, different nomograms as prediction models have been studied.[8,43–45] However, the clinical utility of these models are limited.[46,49]

The goal of the present study was to identify predictive factors associated with a positive SLN, or factors associated the metastatic involvement of non-SLNs to define a subgroup of patients with operable breast cancer in whom axillary dissection may be safely omitted by using clinicopathologic factors in a single institution series.

Patients and methods

Of 605 patients diagnosed with breast cancer at the Acibadem Bakirkoy Hospital between July 2000 and May 2010, those patients with clinically operable T1–2 N0 invasive breast cancer were reviewed. The study consisted of 332 patients who underwent SLN biopsy with or without axillary dissection. Patients who received primary chemotherapy, or diagnosed with DCIS associated with microinvasion, or with T3 tumors were excluded from the study. Data collected included patients characteristics (age, presentation), tumor characteristics [size, histologic type, nuclear grade (NG), HG, LVI, multifocality/multicentricity, surgical margins, estrogen receptor (ER) status, progesteron receptor (PR) status, HER2-staining, FISH] and characteristics of the SLNs and other axillary lymph nodes (SLN and non-SLN, size and number of involved nodes, size of the metastases, presence of ECI in SLN).

Lymphatic mapping was done with a combined technique of lymphoscintigraphy after radiocolloid injection and subareoler methylene blue injection followed by breast massage. On the day of the surgery, 0.1 ml of Technetium Tc99m was given as peritumoral and/or periareolar intradermal injection. At the time of surgery, 2 ml of methylene blue was also used as subareoler injection followed by breast massage. The sentinel nodes colored with blue dye and/or showed radioactivity with gamma probe were removed, and were sent for intraoperative evaluation by the pathologist. The palpable and suspicious lymph nodes during SLN procedure were also removed and examined perioperatively. Briefly, the sentinel lymph node(s) was bisected fresh along its long axis through the hilus or the entering point of afferent lymphatic if it was colored with blue. The node was sliced in 2 mm thickness. Scrape preparations, made from the hilus and from 2 to 4 faces pairs, were stained with hematoxylin & eosin (H&E). In the presence of suspicious cells, frozen section was performed from the related slice of the lymph node. Finally, the lymph nodes were embedded in paraffin.

If the sentinel nodes were found to be positive for metastatic disease, patients underwent completion axillary dissection. If the frozen section was negative or suspicious for isolated tumor cells, operation was terminated without axillary dissection until the definitive pathological examination of the SLN on paraffin sections was obtained. The entire sentinel lymph nodes were serially sectioned with 50 μm intervals, and two sequential slices with 3 μm thickness were prepared. One of these sequential sections was stained with H&E, and the other one was spared for immunohistochemistry in cases with suspicious atypical cells. A pan-cytokeratin antibody (Novocastra, RTU-PAN-CK, Newcastle, UK) was used for immunohistochemistry staining. The SLN metastases were categorized according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging system[48] as follows: isolated tumor cells (ITC) were defined as isolated tumor cells or clusters ≤0.2 mm in maximum diameter; micrometastases were defined as metastases >0.2 mm but <2 mm; macrometastases as >2 mm.

On paraffin section of breast tumors, immunostains for ER and PR were performed by using ER [Novocastra (6F11), Newcastle, UK] and PR [Novocastra (PGR-312), Newcastle, UK] antibodies, and cases with nuclear staining >10% were considered as positive. HER2 positivity was determined based on immunohistochemistry staining by using HER2-neu antibody [Ventana (HER2-neu 4B5), Tucson, Arizona, USA] or FISH test in selected cases. Tumors were also analyzed according to the new molecular subtypes including luminal A [ER(+) or PR(+), HER2(−)], luminal B [ER(+) or PR(+), HER2(+)], or luminal type [ER(+) or PR(+), HER2(−) or HER2 (+)], HER2-enriched [ER(−), PR(−), HER2(+)] or triple negative [ER(−), PR(−), HER2(−)].[49]

The statistical analyses were performed by the Statistical Package for the Social Sciences (SPSS) program, version 15.0 (SPSS Inc., Chicago, IL, USA). The categorical data was compared by Fisher's exact test to determine the associations of the metastatic involvement of the SLNs or non-SLNs with the clinicopathologic factors including age, primary tumor size, multifocality/multicentricity, histologic tumor type, HG, and NG, lymphovascular invasion, ER and PR status, size and number of the SLN metastases, and ECI in SLN. The statistical significance was considered if the *P*-value was equal or less than 0.05. Factors that were found potentially significant in univariate analyses were further analyzed by logistic regression model to identify the independent factors ascociated with the SLN positivity or the non-SLN metastases, and for each factor in the model, the likelihood of positive SLNs or non-SLNs was estimated by the odds ratio (OR) and 95% CI.

Results

Of 605 patients diagnosed with breast cancer between July 2000 and May 2010, 332 patients with clinically operable T1–2 N0 invasive breast cancer underwent SLN biopsy with or without axillary dissection. The SLNs were found to be involved with tumor cells in 136 patients (41%). Of those, 36 patients (26.5%) had micrometastases (≤2 mm), whereas 82 patients (60.3%) were found to have macrometastases (>2 mm). Eighteen patients (13.2%) had isolated tumor cells (ITC) detected by H&E staining or immunohistochemistry (≤0.2 mm). Completion of axillary dissection was not performed in 20 patients with either ITC ($N = 8$) or micrometastases ($N = 10$) or macrometastases ($N = 2$). The remaining 116 patients with SLN involvement underwent axillary lymph node dissection.

Patients with T2 tumors, lymphovascular invasion, high histologic grade or intermediate & high nuclear grade were more likely to have a positive SLN (Table 1). Clinicopathological factors including age more than 50, multifocality/multicentricity, hormone receptor status along with HER2-overexpression (luminal type, HER2-enriched, triple-negativity) were not statistically significantly associated with SLN involvement in our study (Table 1). Tumor characteristics such as ER- or PR-positivity, luminal A or B type or HER2 positivity were also not found to be statistically significantly associated with a positive SLN (data not shown). In logistic regression model, patients with T2 tumors (OR = 3.2; 95% CI, 1.74–5.58), or with lymphovascular invasion (OR = 8.0; 95% CI, 4.44–14.27), or with invasive ductal cancer (OR = 2.92; 95% CI, 1.1–8.0) were more likely to have a positive SLN (Table 2).

Of 116 patients with SLN involvement who underwent ALND, those with macrometastasis in SLN, or with more than 1 SLN involvement or with extracapsular invasion of SLN were more likely to have a non-SLN metastasis (Table 3). The other factors including NG, HG, lymphovascular invasion, multifocality/multicentricity, hormone receptor status along with HER2-overexpression (luminal type, HER2-enriched, triple-negativity) were not statistically significantly associated with non-SLN involvement in this study

Table 1
Univariate analyses for clinicopathologic factors associated with the sentinel lymph node (SLN) metastasis in patients with operable breast cancer ($N = 332$).

Factors	SLN-negative (%) ($N = 198$)	SLN-positive (%) ($N = 134$)	*P*-value
Age			
<50	83 (55.3%)	67 (44.7%)	0.220
≥50	113 (61.1%)	69 (37.9%)	
Multifocality/multicentricity			
(+)	39 (60.9%)	25 (39.1%)	0.999
(−)	159 (58.9%)	111 (41.1%)	
Tumor size			
T_1	153 (68.9%)	69 (31.1%)	0.0001
T_2	43 (39.1%)	67 (60.9%)	
Histologic grade			
Low & intermediate	119 (64.7%)	65 (35.3%)	0.004
High	62 (48.1%)	67 (51.9%)	
Nuclear grade			
Low	17 (81%)	4 (19%)	0.038
Intermediate & high	171 (56.4%)	132 (43.6%)	
Lymphovascular invasion			
(−)	159 (75.7%)	51 (24.3%)	0.0001
(+)	27 (24.8%)	82 (75.2%)	
Tumor histology			
Invasive ductal cancer	164 (56.9%)	124 (43.1%)	0.05
Invasive lobular and other (tubular, metaplastic, etc.)	32 (72.7%)	12 (27.3%)	
Luminal type (ER+ and/or PR+)			
(+)	92 (54.4%)	77 (45.6%)	0.263
(−)	23 (65.7%)	12 (34.3%)	
HER2-enriched (ER−/PR−, HER2+)			
(+)	8 (66.6%)	4 (33.3%)	0.557
(−)	105 (44.1%)	83 (42.5%)	
Triple negatif (ER−, PR−, HER2−)			
Yes	15 (62.2%)	8 (37.8%)	0.504
No	100 (55.2%)	81 (44.8%)	

Unknown data were excluded form the analyses.

(Table 3). Similarly, tumor characteristics such as luminal A or B type, or ER- or PR- or HER2-positivity were not statistically significantly found to be associated with non-SLN positivity (data not shown). However, finding of ITC or micrometastasis (OR = 0.23; 95% CI, 0.07–0.80), or absence of extracapsular invasion in SLN (OR = 0.25; 95% CI, 0.09–0.66) were the only significant predictive factors of not having a non-SLN metastasis in logistic regression analysis (Table 4). The non-SLN involvement rates were 10%, 11.5% and 50% in patients with ITC, micrometastasis and macrometastasis, respectively (Table 3). In subgroup analysis of patients with ITC or micrometastases, patients with T1 tumors were less likely to

Table 2
Multivariate analysis for potentially significant clinicopathologic factors predicting the SLN metastasis in patients with operable breast cancer ($N = 332$).

Factors	Odds ratio	95% Confidence interval	*P*-value
T2 vs T1	3.12	1.74–5.58	0.0001
LVI (+) vs LVI (−)	8.0	4.44–14.27	0.0001
Invasive ductal cancer vs other (lobular, tubular, metaplastic, etc.)	2.92	1.1–8.0	0.038
High HG vs low & intermediate histologic grade (HG)	1.19	0.67–2.1	0.553
Intermediate & high nuclear grade (NG) vs low NG	2.1	0.43–10.0	0.369

Table 3
Univariate analyses for patient and tumor and sentinel lymph node (SLN) characteristics associated with the non-SLN metastases in T1/T2 breast cancer and positive SLN metastases who underwent completion axillary dissection ($N = 116$).

Factors	Non-SLN-negative (%) ($N = 72$)	Non-SLN-positive (%) ($N = 44$)	*P*-value
Age			
<50	39 (67.3%)	19 (32.7%)	0.339
≥50	33 (56.9%)	25 (43.1%)	
Multifocality/multicentricity			
Yes	10 (50%)	10 (50%)	0.311
No	62 (64.6%)	34 (35.4%)	
Tumor size			
T1	39 (69.6%)	17 (30.4%)	0.127
T2	33 (55%)	27 (45%)	
Histologic grade			
Low & intermediate	36 (70.6%)	15 (29.4%)	0.171
High	35 (56.5%)	27 (43.5%)	
Nuclear grade			
Low & intermediate	29 (60%)	17 (40%)	0.999
High	43 (61.4%)	27 (38.6%)	
Lymphovascular invasion			
(−)	27 (67.5%)	13 (32.5%)	0.421
(+)	43 (58.1%)	31 (41.9%)	
Tumor histopathology			
Invasive ductal	65 (62.5%)	39 (37.5%)	0.764
Invasive lobular and other (tubular, metaplastic, etc.)	7 (58.3%)	5 (41.7%)	
Luminal type (ER+ and/or PR+)			
Positive	43 (63.3%)	25 (36.7%)	0.756
Negative	7 (58.3%)	5 (41.7%)	
HER2-enriched (ER− /PR−, HER2+)			
Positive	3 (75%)	1 (25%)	0.999
Negative	46 (62.2%)	28 (37.8%)	
Triple negative (ER−, PR−, HER2−)			
Yes	4 (50%)	4 (50%)	0.465
No	46 (63.9%)	26 (36.1%)	
Size of the SLN metastasis[a]			
Isolated tumor cells	9 (90%)	1 (10%)	0.0001
Micrometastasis	23 (88.5%)	3 (11.5%)	
Macrometastasis	40 (50%)	40 (50%)	
Number of metastatic SLNs			
1	59 (69.6%)	27 (31.4%)	0.017
>1	13 (43.3%)	17 (56.7%)	
Extracapsular invasion of the SLNs			
(−)	55 (76.4%)	17 (23.6%)	0.0001
(+)	10 (30.3%)	23 (69.7%)	

Unknown data were excluded form the analyses.
[a] Isolated tumor cells (ITC) were defined as isolated tumor cells or clusters ≤0.2 mm in maximum diameter; micrometastases were defined as metastases >0.2 mm but <2 mm; macrometastases as >2 mm.

Table 4
Logistic regression analysis for potentially significant pathologic factors associated with the sentinel lymph node (SLN) predicting the non-SLN metastases.

Factors	Odds ratio	95% Confidence interval	*P*-value
Size of metastasis in SLN: ITC&micrometastasis versus macrometastasis	0.28	0.08–0.99	0.05
Presence of extracapsular invasion: (−) versus (+)	0.24	0.09–0.67	0.006
Number of metastatic SLNs: 1 SLN (+) versus >1 SLN (+)	0.50	0.18–1.36	0.173

have non-SLN metastasis than the patients with T2 (T1, 4.5 % versus T2, 21.4%; OR = 0.17; 95% CI, 0.02–1.88). Furthermore, in subgroup analysis of patients with macrometastasis, those with ECI in SLN were more likely to have non-SLN metastases than patients without ECI in SLN (ECI−, 35% versus ECI+, 70%; OR = 0.24; 95% CI, 0.09–0.64). Among patients with macrometasis without ECI, however, the rate of non-SLN positivity dropped from 35% to 28% when only those with one-SLN involved considered.

Discussion

In more than half of the patients with positive SLN, non-SLNs are free of tumor cells and these patients are prone to morbidity of ALND without any benefit. Therefore, reevaluation of ALND as a standard therapy for SLN-positive patients is needed. Different clinicopathologic factors have been studied in previous studies to spare a subset of patients with SLN positivity from morbidity of axillary dissection.[25–42] The association of tumor size with likelihood of non-SLN metastasis has been documented in numerous studies.[13,15,25–31] Reynolds et al.[27] found that patients with pT1 had a lower risk of non-SLN metastasis than patients with pT2 tumor. Joseph et al.[28] also reported that primary tumor size was a predictor of non-SLN, and patients with T1a, T1b and T1c tumors had 0%, 12%, and 47% metastatic non-SLNs, respectively. Ozmen et al.[31] also demonstrated that tumor size >2 cm was associated with a higher rate of SLN and non-SLN involvement. However, we could not find an association of tumor size with non-SLN involvement in our series, although patients with pT2 were more likely to have SLN metastasis than patients with pT1 in both univariate and multivariate analysis in concordance with other reports.[31–50,51] Similarly, Abdessalam et al.[32] and Rahusen et al.[33] could not demonstrate an association between tumor size and non-SLN involvement in multivariate analyses.

In a metaanalysis by Degnim et al.,[34] it was reported that the presence of any one of the five characteristics (SLN metastasis size >2 mm, the presence of extranodal extension in the SLN, tumor size >2 cm, >1 positive SLN, or LVI present in the primary tumor) resulted in >2-fold increase in the likelihood of additional metastasis in the non-SLN. Based on this metaanalysis, the size of the metastatic focus in the SN appears to demonstrate the strongest association with the likelihood of positive non-SLN. Rutledge et al.[35] reported significantly lower rate of non-SLN positivity with SLN micrometastasis than in patients with macrometastatic SLNs (5% vs. 64%) at the intraoperative consult with pathology. Similarly, Fournier et al.[36] found that only macrometastatic disease in the SLN was significantly associated with the involvement of the non-SLNs in multivariate analysis. Only one patient out of 21 patients with micrometastatic SLN had non-SLN metastasis compared to 14 patients out of 26 patients with SLN macrometastasis. In concordance with all these studies, we also found that finding of ITC or micrometastasis in SLNs was a strong predicting factor of not having a non-sentinel lymph node metastasis in both univariate and multivariable analysis.

Rahusen et al.[33] suggested that defining cut off point for micrometastasis in the SLN as <1 mm would result in better discrimination of low risk patients for non-SLN metastasis. He reported non-SLNs were found to be positive in 27% of the patients with SLN metastasis <1 mm, whereas 50% of the patients with SLN metastasis ≥1 mm had non-SLN involvement. Their study was supported by Viale et al.[37] who focused on SLN metastasis ≤2 mm. They subdivided patients by metastasis size in 0.3 mm increments, and found that the proportion for patients with positive non-SLNs was ranging from 13 to 17% for subgroups ≤1 mm compared to the subgroups in which the metastasis was 1–2 mm with a non-SLN involvement ranging from 33% to 38%. Van Deurzen et al.[14] reported that the non-SLN metastasis rates were 12.5%, 23%, and 48% in patients with SLN with ITC, micrometastasis, and macrometastasis, respectively. Menes et al.[38] showed that non-SLN involvement was present in 46% of the patients with SLN metastasis >2 mm in diameter compared to 20% of patients with smaller metastasis. Additionally, 19% of patients with isolated tumor cells (SLN metastasis ≤0.2 mm) harbored non-SLN metastasis. Similar to these studies, the non-SLN involvement rates were found to be 10%, 11.5% and 50% in patients with ITC, micrometastasis and macrometastasis, respectively, in our series.

Along with the size of metastasis in SLN, extracapsular invasion in SLN was also demonstrated as one of the strongest predictors that increased the likelihood of identifying additional node metastasis on subsequent axillary dissection as reported by others.[31,34,52] Ozmen et al reported a significantly increased non-SLN positivity in the presence of extracapsular invasion in the SLN compared to others without extracapsular invasion (65.4% vs 33.3%, respectively). Similarly in our study, almost 70% of patients with extracapsular invasion had non-SLN positivity while 23.6% of patients without extracapsular invasion were found to have non-SLN metastasis.

The nodal ratio has been shown to be an important determinant for predicting additional nodal disease as established by several mathematical models.[8,25,38] Wong et al.[26] and Chu et al.[39] both reported higher rates of non-SLN positivity in patients with >1 positive SLNs compared to patients with 1 positive SLN (>1 SLN+, 50% and 51%, vs 1 SLN+, 32% and 30%, respectively). Viale et al.[37] also found that involvement of more than one SLN was an independent predictor of non-SLN metastasis. Consistent with these studies, we also demonstrated that patients with more than one SLN involvement were more likely to have non-SLN metastases than patients with one SLN involvement (1 SLN+, 56.7% vs >1 SLN+, 31.4%; respectively). However, this difference was not found to be statiscally significant in multivariate analysis.

Another parameter that was associated with a higher risk of non-SLN involvement was high HG although we could not find any association between HG and non-SLN positivity as previously reported by others[15,25–27,32,33,40] while some studies found it as a statiscally significant predictive factor.[29,42] Furthermore, LVI has been found to be correlated with non-SLN positivity by some authors[25,29,32,36,40] while some others reported results without any statistical significance.[27,28,31,33] In our study, we also could not demonstrate any association between LVI and non-SLN involvement while we showed that presence of LVI was significantly associated with SLN metastases as previously reported.[31,50,51]

Based on the clinicopathologic factors investigated to predict the non-SLN metastasis, Van Zee et al.[8] published a nomogram to calculate the likelihood of metastasis in non-SLN. Size, type and grade of tumor, LVI, multifocality, estrogen receptor status, method of detecting metastases in SLN, and number of positive and negative SLNs were included whereas size of the nodal metastasis was

not used. This nomogram was validated in different studies.[43,44] Authors from Memorial Sloan-Kettering Cancer Center suggested that this nomogram failed when micrometastatic SLNs were considered, and a different model might be needed for this group of patients.[44] Kohrt et al.[45] devised an online calculator that included primary tumor size, LVI and size of the SLN metastasis. The authors emphasized synergistic interaction between these parameters. However, the utility of these nomograms are very limited because most women with invasive cancer undergo axillary dissection in the same session, in case, the SLN is positive for metastasis. LVI, extranodal extension, size of the largest focus of nodal metastases, ER status are generally not known during the first operation.[46,47]

Some have proposed that ALND may be omitted in patients with T1 tumors and SLN micrometastasis.[27,35,36,39] Therefore, we further analyzed the subgroup of patients with ITC or micrometastases. Patients with T1 tumors were less likely to have non-SLN metastasis than the patients with T2 as expected (T1, 4.5% versus T2, 20%) in our study. The ACOSOG Z0011 study has recently been groundbreaking and practice changing in this area.[6,23] They reported that 27% of the patients in ALND arm had non-SLN metastases. Regional recurrence rates were similar between ALND arm and SLN only arm after a median follow up time of 6.3 years. The authors suggested that not all non-SLN metastases develop into clinically detectable disease. However, the patients in this trial were a favorable population: 70% had T1 tumors, 83% had ER positive disease, and 41% had small volume metastases, i.e. micrometastases or ITC.[23] Patients with high tumor burden were not randomized to SLNB only group to decrease the risk of treatment failure. These highly selected patients all had breast conservation with whole breast irradiation (=breast conservative therapy; BCT) along with systemic therapy including chemotherapy.[23] Recent findings of the International Breast Cancer Study Group trial 23-01 that only included patients with micrometastatic disease are also comparable with the ACOSOG Z0011 study.[23] All these findings suggest that axillary dissection could be safely omitted in patients with BCT when the non-SLN positivity is expected to be less than 27% in the worst scenario. In our study, the non-SLN involvement was found to be 28% when only those patients with macrometastasis without ECI and those with only one SLN involved considered. Therefore, all these studies and our results suggest that patients with ITC or micrometastases, or patients with macrometastasis with favorable factors such as absence of ECI in SLN or those with only one SLN involved might be the best candidates not to proceed with the completion ALND in patients with BCT. However, there is still a gray zone from a surgical and a radiation oncologist perspective what to do in patients with macrometastases and unfavorable factors that should be carefully discussed with the patients even though the systemic therapy approaches do not often change.

The ACOSOG Z0011 study did not include the patients undergoing mastectomy, lumpectomy without radiotherapy, or those treated with partial breast irradiation. In these patients, ALND still remains to be the standard care when SLN is positive for metastasis.[6]

Conclusions

Our findings indicate that size of metastasis and extracapsular invasion of SLN are the strongest predictors of non-SLN metastases. Our results suggest further axillary surgery could be best omitted in patients with small size tumors and with ITC or micrometastasis in SLN among those with mastectomy. However, in patients with BCT, completion ALND could be safely omitted among those with ITC or micrometastases or with macrometastases without unfavorable factors such as ECI in SLN. Validation of nomograms including different clinicopathologic factors or biological markers are still needed to be studied in patients in this gray zone including patients with BCT and macrometastasis in SLN or who will undergo mastectomy to identify those patients with a minimal risk for non-SLN metastasis to omit ALND.

Conflict of interest statement

None declared.

References

1. Harlow SP, Krag DN, Julian TB, et al. Prerandomization surgical training for the national surgical adjuvant breast and bowel project (NSABP) B-32 trial: a randomized phase III clinical trial to compare sentinel node resection to conventional axillary dissection in clinically node-negative breast cancer. *Ann Surg* 2005;**241**:48–54.
2. Straver ME, Meijnen P, van Tienhoven G, et al. Sentinel node identification rate and nodal involvement in the EORTC 10981-22023 AMAROS trial. *Ann Surg Oncol* 2010;**17**:1854–61.
3. Straver ME, Meijnen P, van Tienhoven G, et al. Role of axillary clearance after a tumor-positive sentinel node in the administration of adjuvant therapy in early breast cancer. *J Clin Oncol* 2010;**28**:731–7.
4. Veronesi U, Viale G, Paganelli G, et al. Sentinel lymph node biopsy in breast cancer: ten-year results of a randomized controlled study. *Ann Surg* 2010;**251**:595–600.
5. Erb KM, Julian TB. Completion of axillary dissection for a positive sentinel node: necessary or not? *Curr Oncol Rep* 2009;**11**:15–20. Review.
6. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA* 2011;**305**:569–75.
7. van Iterson V, Leidenius M, Krogerus L, von Smitten K. Predictive factors for the status of non-sentinel nodes in breast cancer patients with tumor positive sentinel nodes. *Breast Cancer Res Treat* 2003;**82**:39–45.
8. Van Zee KJ, Manasseh DME, Bevilacqua JL, et al. A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. *Ann Surg Oncol* 2003;**10**:1140–51.
9. Degnim AC, Reynolds C, Pantvaidya G, et al. Nonsentinel node metastasis in breast cancer patients: assessment of an existing and a new predictive nomogram. *Am J Surg* 2005;**190**:543–50.
10. Chagpar AB, Scoggins CR, Martin II RC, et al. University of Louisville breast sentinel lymph node study. Prediction of sentinel lymph node-only disease in women with invasive breast cancer. *Am J Surg* 2006;**192**:882–7.
11. Viale G, Maiorano E, Pruneri G, et al. Predicting the risk for additional axillary metastases in patients with breast carcinoma and positive sentinel lymph node biopsy. *Ann Surg* 2005 Feb;**241**(2):319–25.
12. Nos C, Harding-MacKean C, Fréneaux P, Trie A, Falcou MC, Sastre-Garau X, et al. Prediction of tumor involvement in remaining axillary lymph nodes when the sentinel node in a women with breast cancer contains metastases. *Br J Surg* 2003;**90**:1354–60.
13. Houvenaeghel G, Nos C, Mignotte H, et al. Micrometastases in sentinel lymph node in a multicentric study: predictive factors of nonsentinel lymph node involvement–Groupe des Chirurgiens de la Federation des Centres de Lutte Contre le Cancer. *J Clin Oncol* 2006;**24**:1814–22.
14. van Deurzen CH, van Hillegersberg R, Hobbelink MG, Seldenrijk CA, Koelemij R, van Diest PJ. Predictive value of tumor load in breast cancer sentinel lymph nodes for second echelon lymph node metastases. *Cell Oncol* 2007;**29**:497–505.
15. Cserni G, Gregory D, Merletti F, et al. Meta-analysis of non-sentinel node metastases associated with micrometastatic sentinel nodes in breast cancer. *Br J Surg* 2004;**91**:1245–52.
16. Andersson Y, Frisell J, Sylvan M, de Boniface J, Bergkvist L. Breast cancer survival in relation to the metastatic tumor burden in axillary lymph nodes. *J Clin Oncol* 2010;**28**:2868–73.
17. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Eng J Med* 2002;**347**:567–75.
18. Krag DN, Anderson SJ, Julain TB, et al. Sentinel-lymph-node resection compared with conventinel axillary-lymph-node dissection in clinially node-negative patients with breast cancer: overall survival findings from the NSABP-32 randomised phase 3 trial. *Lancet Oncol* 2010;**11**:927–33.
19. Wernicke AG, Goodman RL, Turner BC, et al. A 10-year follow-up of treatment outcomes in patients with early breast cancer and clinically negative axillary nodes treated with tangential breast irradiation following sentinel lymph node dissection or axillary clearance. *Breast Cancer Res Treat* 2011;**125**:893–902.
20. Veronesi U, Orecchia R, Zurrida S, et al. Avoiding axillary dissection in breast cancer surgery: a randomized trial to assess the role of axillary radiotherapy. *Ann Oncol* 2005;**16**:383–8.
21. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol* 2008;**26**:778–85.

22. Martelli G, Boracchi P, De Palo M, et al. A randomized trial comparing axillary dissection to no axillary dissection in older patients with T1N0 breast cancer: results after 5 years of follow-up. *Ann Surg* 2005;**242**:1–6.
23. Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American college of surgeons oncology group Z0011 randomized trial. *Ann Surg* 2010;**252**:426–32.
24. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, et al.International Breast Cancer Study Group Trial 23-01 Investigators. S3-1. Update of international breast cancer study group trial 23-01 to compare axillary dissection versus no axillary dissection in patients with clinically node negative breast cancer and micrometastases in the sentinel node. CTRC-AACR San Antanio breast cancer symposium, San Antanio, Texas, USA; December 6–10, 2011.
25. Hwang RF, Krishnamurthy S, Hunt KK, et al. Clinicopathologic factors predicting involvement of nonsentinel axillary nodes in women with breast cancer. *Ann Surg Oncol* 2003;**10**:248–53.
26. Wong SL, Edwards MJ, Chao C, et al. Predicting the status of the nonsentinel axillary nodes. *Arch Surg* 2001;**136**:563–8.
27. Reynolds C, Mick R, Donohue JH, et al. Sentinel lymph node biopsy with metastasis:can axillary dissection be avoided in some patients with breast cancer? *J Clin Oncol* 1999;**17**:1720–6.
28. Joseph KA, El-Tamer M, Komenaka I, Troxel A, Ditkoff BA, Schnabel F. Predictors of nonsentinel node metastasis in patients with breast cancer after sentinel node metastasis. *Arch Surg* 2004;**139**:648–51.
29. Turner RR, Ku Chu, Qi K, Hansen NM, Glass EC, Giuliano AE. Pathologic features associated with nonsentinel lymph node metastases in patients with metastatic breast carcinoma in a sentinel lymph node. *Cancer* 2000;**89**: 574–81.
30. Kamath VJ, Giuliano R, Dauway EL, et al. Characteristics of the sentinel lymph node in breast cancer predict further involvement of higher-echelon nodes in the axilla: a study to evaluate the need for complete axillary lymph node dissection. *Arch Surg* 2001;**136**:688–92.
31. Ozmen V, Karanlik H, Cabioglu N, et al. Factors predicting the sentinel and non-sentinel lymph node metastases in breast cancer. *Breast Cancer Res Treat* 2006;**95**:1–6.
32. Abdessalam SF, Zervos EE, Prasad M, et al. Predictors of positive axillary lymph nodes after sentinel lymph node biopsy in breast cancer. *Am J Surg* 2001;**182**:316–20.
33. Rahusen FD, Torrenga H, van Diest PJ, Pijpers R, van der Wall E, Licht J, et al. Predictive factors for metastatic involvement of nonsentinel nodes in patients with breast cancer. *Arch Surg* 2001;**136**:1059–63.
34. Degnim AC, Griffith KA, Sabel MS, et al. Clinicopathologic features of metastasis in nonsentinel lymph nodes of breast carcinoma patients: a metaanalysis. *Cancer* 2003;**98**:2307–15.
35. Rutledge H, Davis J, Chiu R, Cibull M, Brill Y, McGrath P, et al. Sentinel node micrometastasis in breast carcinoma may not be an indication for complete axillary dissection. *Mod Pathol* 2005;**18**:762–8.
36. Fournier K, Schiller A, Perry RR, Laronga C. Micrometastasis in the sentinel lymph node of breast cancer does not mandate completion axillary dissection. *Ann Surg* 2004;**239**:859–65.
37. Viale G, Maiorano E, Mazzarol G, et al. Histologic detection and clinical implications of micrometastasis in axillary sentinel lymph nodes for patients with breast carcinoma. *Cancer* 2001;**92**:1378–84.
38. Menes TS, Tartter PI, Mizrachi H, Constantino J, Estabrook A, Smith SR. Breast cancer patients with pN0(i+) and pN1(mi) sentinel nodes have high rate of nonsentinel node metastases. *J Am Coll Surg* 2005;**200**:323–7.
39. Chu KU, Turner RR, Hansen NM, Brennan MB, Bilchik A, Giuliano AE. Do all patients with sentinel node metastasis from breast carcinoma need complete axillary node dissection? *Ann Surg* 1999;**229**:536–41.
40. Weiser MR, Montgomery LL, Tan LK, Susnik B, Leung DY, Borgen PI, et al. Lymphovascular invasion enhances the prediction of non-sentinel node metastases in breast cancer patients with positive sentinel nodes. *Ann Surg Oncol* 2001;**8**:145–9.
41. Stitzenberg KB, Meyer AA, Stern SL, et al. Extracapsular extension of the sentinel lymph node metastasis: a predictor of nonsentinel node tumor burden. *Ann Surg* 2003;**237**:607–12.
42. den Bakker MA, van Weeszenberg, de Kanter AY, Beverdam FH, Pritchard C, van der Kwast TH, et al. Non-sentinel lymph node involvement in patients with breast cancer and sentinel node micrometastasis; too early to abandon axillary clearance. *J Clin Pathol* 2002;**55**:932–5.
43. Lambert LA, Ayers GD, Hwang RF, et al. Validation of a breast cancer nomogram for predicting nonsentinel node metastases after a positive sentinel lymph node biopsy. *Ann Surg Oncol* 2006;**13**:310–20.
44. Alran S, DeRycke Y, Fourchotte V, et al. Validation and limitations of use of a breast cancer nomogram predicting the likelihood of non-sentinel node involvement after positive sentinel node biopsy. *Ann Surg Oncol* 2007;**14**:2195–201.
45. Kohrt HE, Olshen RA, Berma HR, et al. New models and online calculator for predicting non-sentinel lymph node status in sentinel lymph node positive breast cancer patients. *BMC Cancer* 2008;**8**:66.
46. Chagpar AB, Scoggins CR, Martin 2nd RC, et al. University of Louisville breast sentinel lymph node study. Predicting patients at low probability of requiring postmastectomy radiation therapy. *Ann Surg Oncol* 2007;**14**:670–7.
47. Chagpar AB, McMasters KM. Comparing prediction models: the distinction between clinical and statistical significance. *Ann Surg Oncol* 2011;**18**(Suppl. 3):S265.
48. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. *AJCC cancer staging handbook*. 7th ed. Springer; 2009.
49. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci USA* 2001;**98**:10869–74.
50. Wada N, Imoto S, Yamauchi C, Hasebe T, Ochiai A. Predictors of tumour involvement in remaining axillary lymph nodes of breast cancer patients with positive sentinel lymph node. *Eur J Surg Oncol* 2006;**32**:29–33.
51. Rivers AK, Griffith KA, Hunt KK, et al. Clinicopathologic features associated with having four or more metastatic axillary nodes in breast cancer patients with a positive sentinel lymph node. *Ann Surg Oncol* 2006;**13**:36–44.
52. Saidi RF, Dudrick PS, Remine SG, Mittal VK. Nonsentinel lymph node status after positive sentinel lymph node biopsy in early breast cancer. *Am Surg* 2004;**70**:101–5.