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ARTICLE

Sentinel Lymph Node Biopsy in Staging Small (up to 15 mm) Breast Carcinomas. Results from a European Multi-institutional Study

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Sentinel lymph node (SLN) biopsy has become the preferred method for the nodal staging of early breast cancer, but controversy exists regarding its universal use and consequences in small tumors. 2929 cases of breast carcinomas not larger than 15 mm and staged with SLN biopsy with or without axillary dissection were collected from the authors' institutions. The pathology of the SLNs included multilevel hematoxylin and eosin (HE) staining. Cytokeratin immunohistochemistry (IHC) was commonly used for cases negative with HE staining. Variables influencing SLN involvement and non-SLN involvement were studied with logistic regression. Factors that influenced SLN involvement included tumor size, multifocality, grade and age. Small tumors up to 4 mm (including in situ and microinvasive carcinomas) seem to have SLN involvement in less than 10%. Non-SLN metastases were associated with tumor grade, the ratio of involved SLNs and SLN involvement type. Isolated tumor cells were not likely to be associated with further nodal load, whereas micrometastases had some subsets with low risk of non-SLN involvement and subsets with higher proportion of further nodal spread. In situ and microinvasive carcinomas have a very low risk of SLN involvement, therefore, these tumors might not need SLN biopsy for staging, and this may be the approach used for very small invasive carcinomas. If an SLN is involved, isolated tumor cells are rarely if ever associated with non-SLN metastases, and subsets of micrometastatic SLN involvement may be approached similarly. With macrometastases the risk of non-SLN involvement increases, and further axillary treatment should be generally indicated. (Pathology Oncology Research Vol 13, No 1, 5–14)

Key words: Sentinel lymph node, non-sentinel lymph node, breast cancer, pT1

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Abbreviations

ALND: axillary lymph node dissection, DCIS: ductal carcinoma in situ, ITC: isolated tumor cells, LVI: lymphovascular invasion, SLN: sentinel lymph node, SLNB: sentinel lymph node biopsy

Introduction

Axillary dissection has long been part of the standard surgical treatment of breast carcinoma. It was first conceived as a therapeutic intervention eliminating disease from the regional lymph nodes,[1] but later, with the formulation of the systemic theory of breast cancer,[2] it became for many a surgical staging procedure only. With this in mind, and the fact that more and more patients are diagnosed at a stage where nodal involvement is not yet present, more conservative approaches to the axilla have been tested: these include axillary sampling,[3-5] sentinel lymph node (SLN) biopsy (SLNB) with different tracers[6-8] and axillary sparing.[9]

There is at least some evidence from the radiotherapy[10-13] and the surgical[14] literature, including the most recent Oxford overview,[15] that locoregional treatment, including the treatment of the axilla has some prognostic benefit. The benefits of regional treatment can be expected only in patients who have metastatic involvement of the axillary lymph nodes. SLNB has become a very popular, low morbidity method for the staging of patients with breast carcinoma, and has given rise to controversies for the indication of this procedure. For example, it has been widely accepted that axillary dissection should not be performed in patients with the earliest stage of breast cancer, ductal carcinoma in situ (DCIS),[16,17] but some investigators have found surprisingly high rates of axillary SLN involvement with this disease (6-13%),[18-20] or in microinvasive cancer (10-20%)[19-21] which is often managed the same way as DCIS. The view that SLNB should be advised to nearly all patients with breast carcinoma is not uncommon.

When an SLN is found to be positive the question whether the axilla should be further treated (by dissection or radiotherapy) is also controversial. SLN metastatic volume (reflected by metastasis size and/or the number of involved SLNs) and primary tumor size [22] have often been found to be the two most important factors associated with the involvement of further axillary lymph nodes. Some studies have concluded that small tumors, if associated with low volume SLN involvement (generally classified as micrometastasis) need no further axillary treatment, whereas others have found that even micrometastases may be associated with certain risk of further nodal involvement,[23-25] which would mandate their treatment. Without a reliable selection tool this would lead to the "treatment" of all patients, including some 70-80% of patients who are overtreated by this policy as they have no additional axillary lymph node metastases. This contradiction has generated the search for selection tools that could allow an acceptable identification of the group of patients with low risk of further nodal involvement. The nomogram created at the Memorial Sloan-Kettering Cancer Center [26] seems to be useful for this aim,[27,28] although it was found to underestimate the risk of some patients.[29-31]

In the present study we evaluated a multi-institutional cohort of small breast carcinomas up to and inclusive of 15 mm in greatest dimension in order to assess the risks of axillary SLN involvement, and non-SLN involvement if the SLN was involved.

Materials and Methods

The European Working Group for Breast Screening Pathology has dealt with several issues concerning SLNB,[32-35] in order to formulate the related European guidelines.[36] Contributors of the previous works were asked to participate in the present study on a voluntary basis. From all breast carcinoma cases that have been staged by SLNB or SLNB and further axillary surgery, files of patients with DCIS or invasive tumors not larger than 15 mm had to be analyzed for the following data entered in the study: the age of the patients, the histological type of the tumor, whether the tumor was unifocal or multiple, the invasive tumor size, the number of SLNs removed and found to be involved, the type of SLN involvement according to the TNM categories,[37] the method of identification of SLN involvement (hematoxylin and eosin staining – HE or cytokeratin immunohistochemistry – IHC), whether axillary dissection was performed or not, and the number of non-SLN removed and found positive.

Microinvasive carcinomas were defined as in situ carcinomas with invasive focus or foci none of which was greater than 1 mm.[36,37] Tumor size of the invasive component was rounded to the closest mm, and whenever there were multiple invasive tumor foci, the size of the largest was considered as tumor size. By definition, DCIS had 0 mm invasive size, as well as the few microinvasive (pT1mic) or pT1a invasive carcinomas that were smaller than 0.5 mm and were therefore rounded down to 0. The carcinomas with 1 mm size in this study include both pT1mic carcinomas and a few pT1a tumors, depending on whether or not DCIS was identified. No distinction between multifocal or multicentric tumors was made, all tumors with multiple invasive foci were categorized as multiple. Histological typing was done according to standard guidelines.[38,39]

For the purpose of this study, any tumor cell in a SLN was considered a positive finding. Nodal involvement was then categorized into ITCs, micrometastases or macrometastases according to the definitions of these categories.[34,37,40-42]

The different participating institutions had varying protocols for the SLN work-up, but all departments embedded the whole SLN. SLNs greater than 5 mm were sliced into pieces and all departments used the approach of multilevel HE staining, and most applied cytokeratin immunostains routinely if the HE slides were negative. Whenever IHC

was not used in the analysis, node negativity was considered as negative by HE, whereas in other cases it was recorded as node negativity with IHC.

Statistical analyses were performed with the help of the OpenStat4 software.[43] Multivariate logistic regression models were used to define the variables influencing either SLN involvement or non-SLN involvement. The significance levels were set at $p<0.05$.

Results

Altogether, the 14 participating institutions entered 2929 tumors not larger than 15 mm in the analysis (*Table 1*). All but two participating institutions contributed with their data on breast tumors not larger than 15 mm; data from Strasbourg included only tumors not larger than 10 mm, and data from Coimbra included only data on tumors with positive SLNs, and therefore this later subset was only included in the analysis for non-SLN involvement.

The mean and median ages of the patients were both 58 year (range 22 to 87 years). The basic characteristics of the tumors are listed in *Tables 1 and 2*. Histological types listed under "other special types" in *Table 2* included 26 invasive micropapillary, 12 medullary, 11 apocrine, 6 mixed invasive micropapillary, 3 metaplastic, 2 glycogen-rich, 2 neuroendocrine, 1 lymphoepithelial, 1 atypical medullary and 1 adenoid cystic carcinoma. Altogether 663 patients underwent axillary dissection, 160 of them had no metastases in the SLNs, and had the completion axillary procedure as a routine operation during the learning period of SLNB. In contrast 137 patients with involved SLNs did not have an axillary dissection either because of low perceived risk and their own wish, or because of participation in a study comparing axillary clearance with axillary radiotherapy in SLN-positive patients (European Organization for Research and Treatment of Cancer /EORTC/ trial 10981 "After Mapping of the Axilla: Radiotherapy Or Surgery" – AMAROS). Five patients with no information on axillary dissection and positive SLNs were also regarded as having no such a completion procedure, as their data on further nodes were unavailable for analysis. In addition, although a formal axillary dissection was not performed, some (range 1-6; median 1; mean ± SD: 1.9 ± 1.2) non-SLNs were also sampled as part of a rather common practice (Kalmar Hospital) or as technical side products of the SLNB procedure in 256 patients; 5 of these samples contained 1 (4 cases) or 2 (1 case) metastatic lymph nodes. Axillary dissection yielded 1 to 44 (median: 13, mean ± SD: 14.2 ± 6.7) non-SLNs; the number of positive non-SLNs ranged between 0 and 21 (median: 1; mean ± SD: 2.9±3.6 for the non-SLN-positive group including 141 tumors).

Inclusion of the variables in the preliminary, exploratory model suggested that tumor type (with all major types included and the rest represented by only a few cases lumped together as other type), method used for the SLN work-up (HE vs. IHC) and the number of SLNs removed were not significant independent parameters to predict SLN involvement. After the exclusion of these parameters from the final model, tumor size, focality, grade and patients' age remained the significant predictors of SLN involvement (*Table 3*). Tumor size was highly correlated with SLN involvement (coefficient: 0.95 whether or not ITCs were considered as SLN involvement) (*Fig. 1*). DCIS

Table 1. **Basic characteristics of contributed cases per contributing institution**

Department, identified by contributor	*Number of cases entered in this analysis (pTis / pT1mic / pT1a / pT1b / pT1c up to 15 mm)*	*Mean invasive tumor sizes of pT1 tumors in mm (SD)*	*SN positive cases (by HE / by IHC)*
Bianchi	608 (51/0/59/253/245)	9.1 (4.3)	144 (107/35)
Arisio	405 (0/1/53/144/207)	9.8 (4.0)	76 (67/9)
Cserni	392 (40/21/25/106/200)	10.2 (4.0)	111 (80/31)
Peterse	341 (16/1/17/120/187)	10.4 (3.8)	84 (68/16)
Sapino	245 (11/0/23/75/136)	10.5 (3.6)	44 (37/7)
Drijkoningen	207 (43/0/15/96/53)	9.5 (3.0)	44 (39/5)
Kulka	146 (6/5/4/38/93)	10.5 (3.8)	23 (21/2)
Foschini	143 (24/2/16/31/70)	10.4 (4.3)	28 (22/6)
Bellocq	125 (0/0/28/86/11)	7.3 (2.9)	19 (8/11)
Thorstenson	117 (4/0/10/29/74)	11.7 (3.6)	24 (24/na)
Amendoeira	84 (13/0/7/20/44)	9.3 (5.1)	15 (15/na)
Reiner-Concin	66 (2/1/8/14/41)	10.5 (3.4)	16 (13/3)
Decker	39 (8/0/3/18/10)	8.9 (3.4)	3 (3/na)
Figueiredo	11 (0/0/0/3/8)	12.6 (3.1)	11 (7/4)
Total	2929 (218/31/268/1033/1379)	9.4 (4.4)	640 (511/129)

Table 2. **Basic characteristics of the tumors analyzed**

Median (mean; SD) tumor size for all tumors	*10 mm (9.4; 4.4)*
Tumor sizes as pT categories	
pTis	218
pT1mic	31
pT1a	268
pT1b	1033
pT1c (up to and inclusive of 15 mm)	1379
Combined histological grade (Nottingham)	
Grade 1	111
Grade 2	1087
Grade 3	467
Unknown / Not graded (in situ, microinvasive, very small invasive tumors)	264
Invasive tumors by type (excluding microinvasive tumors)	
Invasive ductal carcinomas (no special type)	1714
Invasive lobular carcinomas	191
Tubular/cribriform carcinomas	331/96
Invasive mucinous carcinomas	66
Invasive papillary carcinomas	30
Mixed lobular/tubular/cribriform/mucinous carcinomas	121/36/20/10
Other special type tumors (see text for details)	65
Unifocal tumors	2559
Multiple tumors (multifocal or multicentric)	224
Tumors with no data on focality	135
SLN involvement by ITC / micrometastasis / macrometastasis	71 / 234 / 335
All / SLN-positive patients with axillary clearance	663 / 526
All non-SLN-positive patients	146

cases and microinvasive cases were associated with SLN involvement in 5 (2.2%; 2 ITC detected by IHC, 2 micrometastases detected by IHC and HE, respectively and 1 macrometastasis detected by HE) and 2 (6.5%; 2 micrometastases, each detected by HE) cases, respectively. Axillary dissection was performed on 2 occasions in both categories, with no positive non-SLNs found.

The influence of the histological grade of invasive tumors was less obvious, but well-differentiated tumors were associated with less SLN involvement (*Fig. 2*). Older age was also found to be associated with somewhat lower SLN involvement (*Fig. 3*). Unifocal and multifocal tumors had 21.0% and 33.9% of SLN involvement, respectively. Taking into consideration the good constellation of unifocal and well-differentiated tumors, SLN involvement occurred relatively rarely as illustrated by the cumulative proportion being over 10% at tumor size of 9 mm and reaching a maximum of 16% at tumor size of 15 mm (*Fig. 4*). Well-differentiated multifocal tumors with largest invasive component up to 4 mm had no SLN metastases, but their small number (n=8) did not allow a reliable estimation of SLN involvement in this category; all the other size subsets by mm (tumors 5-15 mm in largest dimension) were characterized by >10% rate of SLN involvement. Higher grade tumors larger than 1 mm in size were generally associated with >10% rate of SLN involvement, but again the numbers for the mm size categories was low, ranging from 13 to 71 for tumors between 2 and 7 mm (with large 95% confidence intervals ranging from ±19.6% to ± 9%), and exceeded a hundred only for larger size categories.

The exploratory model suggested that tumor type, age, method of metastasis detection (HE vs. IHC), method used for the SLN work-up (HE vs. IHC) and focality of the tumors were not significant independent parameters to predict non-SLN involvement (p values >0.3), whereas the SLN involvement type (none vs. ITC vs. micrometastasis vs. macrometastasis), the grade of the primary tumor, the number of removed and involved SLNs were significant.

Table 3. **Factors influencing SLN involvement (logistic regression results)**

	All possible variables included			*Only significant variables included*		
Variable	*OR*	*(95% CI)*	*p*	*OR*	*(95% CI)*	*p*
Focality	1.7087	(1.2876–2.2676)	0.0002	1.7907	(1.3706–2.3396)	<0.0001
Grade	1.3005	(1.1519–1.4682)	<0.0001	1.3035	(1.1551–1.4710)	<0.0001
Method of SLN work-up (HE vs. IHC)	1.2376	(0.8532–1.7951)	0.2612	–		
Tumor size (mm)	1.1611	(1.1296–1.1935)	<0.0001	1.1661	(1.1346–1.1984)	<0.0001
Tumor type	1.0058	(0.9709–1.0420)	0.7462	–	–	–
Number of SLNs removed	0.9863	(0.9086–1.0707)	0.7417	–	–	–
Age (years)	0.9819	(0.9732–0.9906)	<0.0001	0.9825	(0.9740–0.9911)	0.0001

OR: Odds ratio; 95% CI: 95% confidence interval; p: probability values (significance level at p<0.05)

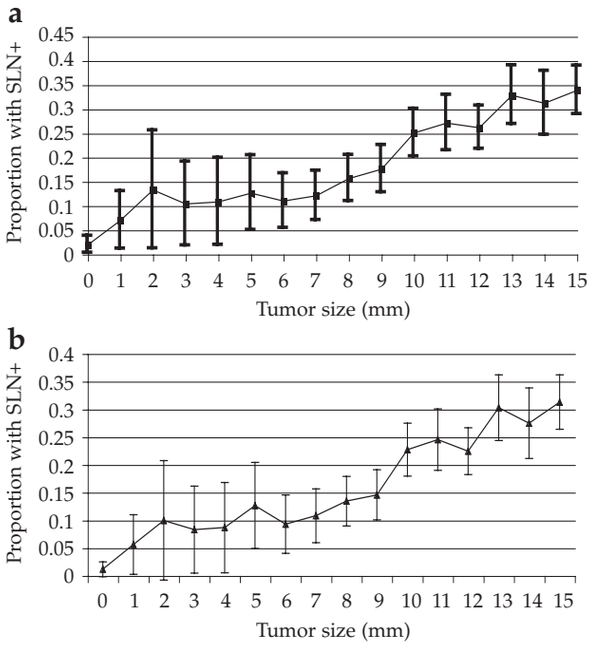

Figure 1. *Proportion of cases with SLN involvement according to tumor size.* ***(a)*** *ITCs considered as SLN involvement.* ***(b)*** *ITCs considered as negative findings. Bars represent 95% confidence intervals. (SLN+: positive sentinel lymph nodes)*

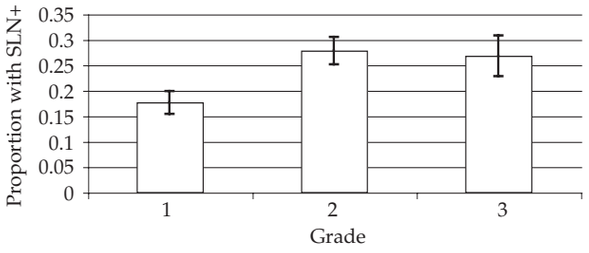

Figure 2. *Proportion of cases with SLN involvement according to histological grade of the tumor. Bars represent 95% confidence intervals. (SLN+: positive sentinel lymph nodes)*

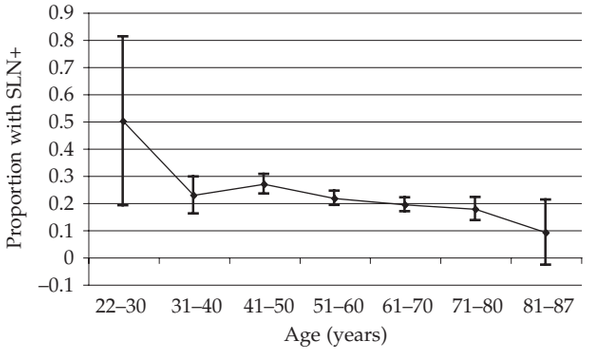

Figure 3. *Proportion of cases with SLN involvement according to patients' age. Bars represent 95% confidence intervals. (SLN+: positive sentinel lymph nodes)*

Interestingly, tumor size was not found to be significant with a p value of 0.1694 (data not shown). On the basis of this analysis and previous works yielding similar resuls,[44-45] the non-correlated values (correlation coefficient: 0.082) of the number of SLNs involved and the number of SLNs analyzed were combined in a single variable, the SLN ratio, used as a transformed value (100 multiplied by the ratio itself; i.e. expressed as a percent-like value) for the analyses. The final model included only the 3 variables which were statistically significant (*Tables 4 and 5*). When tumor size was entered in this final model, it was characterized by an odds ratio of 1.0471 (95% CI: 0.9798-1.1190; p=0.1749), and failed to be significant. Similarly, tumor size would not have been significant, even if it were included as a categorical variable (in situ carcinomas; invasive carcinomas up to 5 mm, larger than 5 mm but not larger than 10 mm, and larger than 10 mm). Despite this lack of significance in the logistic regression analysis, tumor size was correlated with non-SLN involvement (coefficient 0.87) and larger tumors were generally associated with higher rates of non-SLN involvement (*Fig. 5*). Of the 663 patients who had undergone axillary dissection, the proportion of those who underwent this treatment probably as overtreatment (negative status of the non-SLNs) was rather high in the whole series (0.79; 95% CI: 0.76-0.82), but was the highest for the smallest tumors (*Fig. 6*).

The finding of isolated tumor cells in the SLNs carries a low risk of non-SLN metastasis as shown in *Tables 5 and 6*, whereas macrometastatic involvement of the SLNs is associated with a >10% incidence of non-SLN involvement, independently of grade, although higher grade tumors had higher rates of additional lymph node metastases in the axilla. Micrometastases were associated with an intermediate risk of non-SLN involvement, but grade of the tumors did not show any consistent influence on its rate, probably because of the low case numbers even in this large series.

Discussion

Breast cancer screening has lead to the detection of the disease at an earlier stage with less node-positive cases being diagnosed.[46] This has enhanced the search of alternative approaches to axillary staging. At present, SLNB has widely replaced axillary dissection for the staging of clinically node-negative breast carcinoma, but it has several controversial issues.

SLNs have been reported to harbor metastases in up to 6-13% of DCIS cases.[18-20] However, the prognosis of DCIS does not support such a high proportion of nodal involvement, and it has been repeatedly suggested that the definitive diagnosis of DCIS should not lead to axillary surgical staging procedure, including SLNB.[16,17,47] Our data support the latter statement, as SLN involvement was found to be

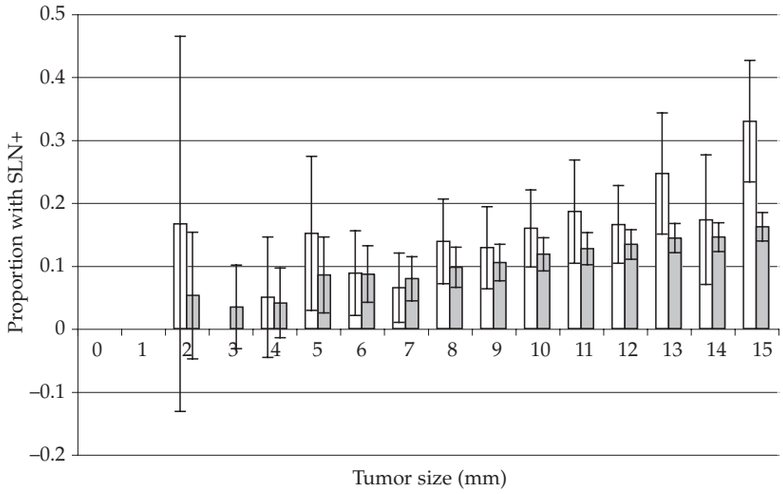

Figure 4. *Proportion (white) and cumulative proportion (dark) of well-differentiated unifocal tumors with SLN involvement in the given size categories. Bars represent 95% confidence intervals. (SLN+: positive sentinel lymph nodes). Note that due to the large confidence interval for very small tumors (very few in number in the series), well-differentiated tumors up to 5 mm in size are rarely associated with SLN involvement, and tumors 5 to 8 mm in size are also more likely to have SLN positivity in less than 10%.*

low (only 2.2%, or 1.4% if the 2 ITCs are not considered) for DCIS. This is in keeping with several other reports suggesting a low rate of nodal involvement.[48-54] The reasons for the discrepancy in reported rates of SLN involvement (high versus low) in DCIS may include tumor cell displacement artefacts interpreted as metastasis, less thorough sampling of the tumor and consequent miss of the invasive component, or the fact that it may be difficult to identify invasion in some poorly differentiated DCIS cases without using multiple IHC stains.[55] Notwithstanding that the majority of the related reports suggest a low frequency of nodal metastasis, SLN biopsy may be performed when mastectomy is done for a disease preoperatively diagnosed as DCIS, or whenever invasive disease is suspected.[47,56] Although the present data are insufficient to support the practice of not performing axillary dissection in the event of positive SLNs and DCIS (only 2 micrometastatic cases had axillary clearance with no additional positive LNs discovered), we believe that this practice is acceptable in the light of the excellent prognosis and low nodal metastatic rate of DCIS reported in studies from before the SLN era.[48,51,57]

Although microinvasive cases were few in this series, it seems that the rate of SLN involvement is somewhat higher (6.5%) than the rate seen in DCIS, and some may find this high enough to justify SLNB. SLN involvement for microinvasive cancers was reported to be higher than for DCIS by several authors,[19-21] and these studies generally reflect a rate of around 10% (3 out of 31[19] and 4 out of 41[21]). The higher rate (20%; 3 out of 15) reported in one series probably reflects low case numbers belonging in this category.[20] Patients' informed decision/consent could use the figure of 7 to 10% derived from this study and others quoted above as an estimate. This is very similar to reported false-negativity rates of the SLNB procedure itself.[32]

Invasive tumor size showed a strong correlation with SLN involvement and, therefore, increasing size was associated with increasing nodal metastasis rate. In this large multi-institutional series, even tumors larger than 2 mm were associated with >10% SLN involvement. More importantly, if ITCs were considered as negative findings, tumors larger than 4 mm were found to have >10% SLN involvement. However, size was not the only factor associated with SLN involvement: in keeping with earlier results, multifocal, grade 2 or 3 tumors and younger (<50 years of age) patients had higher rates of SLN positivity than unifocal, well-differentiated tumors and older patients, respectively.[58] Therefore, on the basis of the cumulative proportion of nodal involvement, it seems that patients having low-grade and unifocal tumors smaller than 10 mm could also be considered for the omission of ALND. This is in keeping with a recent retrospective analysis of 355 cases documenting a low (3%) overall nodal metastasis rate in grade 1 carcinomas without LVI and not larger than 10mm; whereas both the larger size category (11-20 mm) low-grade tumors and the grade 2 tumors of the same size had higher rates of nodal metastasis (12% and 14%, respectively).[59] However, care should be taken with the cumulative figures, which reflect the general practice of lumping tumors of a given pT category together. The cumulative values represent a mean proportion including the lower non-SLN positivity rate of smaller

Table 4. **Factors influencing non-SLN involvement, logistic regression results**

Variable	*OR*	*(95% CI)*	*p*
Grade	1.7330	(1.3247–2.2672)	0.0001
SLN+ ratio	1.0081	(1.0010–1.0152)	0.0250
SLN involvement type	3.9237	(2.9998–5.1321)	<0.0001

OR: Odds ratio; 95% CI: 95% confidence interval; p: probability values (significance level at p<0.05). It must be noted that the OR value seems small for the SLN ratio, but this parameter changes rather abruptly instead of a step-by-step increase.

tumors and the somewhat higher rate of the larger tumors; the smaller 95% confidence intervals of the cumulative values suggest a more reliable estimate, but the individual size group values may still be more valid, especially for the larger tumors having more cases and smaller 95% confidence intervals. *(Fig. 4.)* As the age of the patients proved to be a significant risk factor for SLN involvement, it seems that younger patients (below age 30) could be recommended SLNB even with microinvasive or very small tumors for a safe axillary staging.

Table 5. **Non-SLN involvement rate as a function of variables found significant in the logistic regression model**

	Non-SLN involvement rate	*Comment / explanatory notes*
SLN negative	0.06 *	160/2289 had axillary dissection
SLN with ITC	0 *	26/71 had axillary dissection
SLN with micrometastasis	0.12 *	178/234 had axillary dissection
SLN with macrometastasis	0.37 *	299/335 had axillary dissection
Grade 1	0.03 **	
Grade 2	0.06 **	
Grade 3	0.10 **	
SLN ratio 0-33	0.18 **	
SLN ratio 34-66	0.21 **	
SLN ratio 67-100	0.34 **	

* Only cases with axillary dissection. ** After exclusion of SLN-positive cases without axillary dissection, only for graded invasive tumors (n=2531).

Obviously, lymphovascular invasion (LVI) around the primary tumor, i.e. the presence of tumor cell emboli in the lymphatics is a factor that precedes nodal involvement, as the SLNs are reached via the lymphatic vessels. However, lymphatic involvement is not always seen when nodal metastases are present, and this is simply explained by the fact that histopathologic assessment is based on sampling, and LVI may be too minuscule as a change to be included in the tissue blocks: it must either be extensive for detection (this certainly harbors a much higher chance of nodal metastasis) or be included by chance in the sectioning level examined. It must also be mentioned that the presence of epithelial cells in the lymphatics can also represent tumor cell dislodgement and benign epithelial transport [60-64] which sometimes represents a challenging task to differentiate from tumor emboli. Although this study lacks data on LVI, SLN involvement was found to be so strongly correlated with tumor size that even tumors larger than 1-2 mm (or 4 mm if ITCs were not considered real metastases) had already a substantial proportion (>10%) of SLN involvement. LVI is rather rare in microinvasive tumors and true LVI is by definition absent in DCIS. Therefore, it was not felt that the presence of LVI or its lack could substantially influence the decision on whether or not axillary SLNB should be performed. Should axillary nodal status be required for staging and/or therapeutic decisions, SLNB cannot be obviated in most tumors without a >10% risk of missing nodal involvement; the exceptions might be DCIS and very small invasive carcinomas (up to 4 mm in size, if ITC are not considered positive nodal findings). These results are in keeping with those obtained in a large (n=4351) single institutional series including 1157 pT1a and pT1b tumors, where the rate of SLN involvement was 9.5% for the most favorable combination of predictors (i.e. tumor size not larger than 1 cm, lack of LVI and favorable histologic type).[65]

Most series, similarly to our results, report that the vast majority of patients who undergo axillary dissection because of the finding of positive SLNs are found to have no further metastasis in the axillary lymph nodes. This is why several studies have tried to estimate the risk of non-SLN involvement. A review of many of the earlier studies in this field has formulated that the most important factors influencing non-SLN metastases are SLN metastasis size, the number of SLNs involved, the presence of extracapsular spread, the tumor size and lymphovascular invasion.[22] Of these five parameters, data on LVI and extracapsular invasion were not available. The nodal volume was reflected by the type of SLN involvement as determined by the pN(sn) categories[37] and was found to be the major factor in predicting the risk of further nodal involvement. Nodal volume was also reflected by the number of SLNs involved, however, the number of SLNs removed or uninvolved was also found to be relevant in several studies[26,44] and our series is not an exception in this respect. The number of SLNs involved and removed was not correlated with

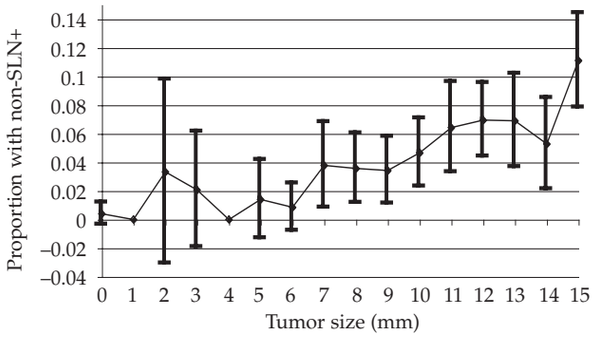

Figure 5. *Proportion of patients with non-SLN involvement according to tumor size. Bars represent 95% confidence intervals. (SLN+: positive sentinel lymph nodes). Note that patients with no further axillary staging after the finding of negative SLNs are also included in this figure.*

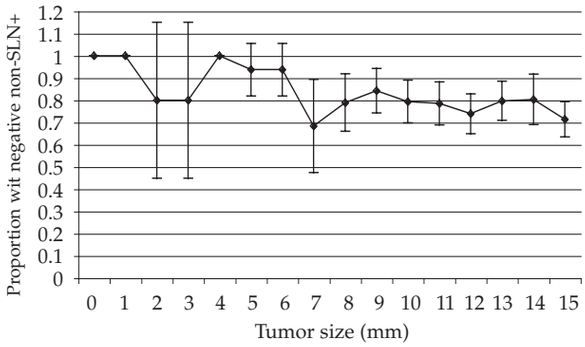

Figure 6. *Proportion of patients with axillary dissection and no further nodal involvement (negative non-SLNs) as a function of invasive tumor size. Bars represent 95% confidence intervals. (SLN+: positive sentinel lymph nodes). Note that patients with no further axillary staging after the finding of negative SLNs are also included in this figure.*

each other and their ratio was used as a single derived factor, found to be significantly associated with non-SLN involvement. This is similar to our previous finding on a single institutional dataset,[44] and to previous observations[45,66] on breast cancer, suggesting that the ratio of involved nodes comprises more prognostic information than the number of involved lymph nodes alone. Accordingly, an increasing SLN ratio was found to be associated with an increasing rate of non-SLN metastasis. Grade was also found to influence the non-SLN metastatic rate: poorly differentiated carcinomas were associated with more metastases.

Considering the three main factors independently influencing the rate of non-SLN involvement, ITCs were practically never associated with further metastases and this is consistent with the findings from the John Wayne Cancer Institute, where 3 out of 61 patients with SLN ITC had additional axillary metastases, and all 3 tumors belonged to the pT2 or pT3 categories.[67] ITC-associated non-SLN metastases were also rare in a recent Dutch study: 2 ITCs and 2 metastases in a set of 54 cases with SLN ITCs.[68] However, there are also reports contradicting our findings. A recent French multicenter study[25] suggested that up to 10% of the cases with SLN involvement detected by IHC had non-SLN metastasis, but the authors of that study could not find any association with the size of SLN involvement (with 0.2 mm as a cut-off value) and the presence of non-SLN metastasis: ITCs and micrometastases in the SLNs were associated with 16% and 14% of further nodal load, respectively. It must, however, be mentioned that the authors had an objective measurement of the SLN metastasis size in only 36% of their cases, and used size as the sole criterion for distinguishing between ITC and micrometastasis,[25] which is not consistent with what was suggested for this distinction by other authors.[34,41] We generally use a more restrictive definition for ITCs, including the lack of parenchymal (extravascular) involvement, associated tissue reaction, adhesion to vessel wall or proliferation.[34,37,41,42]

Similarly to other reports, macrometastatic SLNs were associated with a high rate of non-SLN involvement, suggesting the universal need for further axillary treatment. On the contrary, micrometastatic SLN cases seemed to have relatively low incidence of further axillary nodal deposits (12%), especially in some subsets of better differentiated tumors and lower SLN ratio. However, the case numbers were low as reflected by the wide 95% confidence intervals, and this can probably explain that one of the subsets with the lowest rates of non-SLN involvement was the one with the highest SLN ratio and grade. *(Table 6.)* The reports on the incidence of non-SLN involvement in relation to SLN micrometastases are contradictory, and our results also suggest that the finding of micrometastases in SLNs alone is not sufficient to make a decision about the need of further axillary dissection. This area needs further studies, and it is very likely that some subsets in this group may require axillary dissection on the basis of predictive tools.

Interestingly, although tumor size was somewhat correlated with non-SLN involvement rate, it was not found to be a significant independent predictor of non-SLN involvement in this series. Tumor size generally features as a categorical value in most series, but when we included it as such, it still lacked significance. The lack of significance is probably due to the fact that we analyzed only small tumors, and in this range, tumor size looses its

Table 6. **Non-SLN involvement rate with the combination of different variables found significant in the logistic regression model**

SLN ratio	*ITC Grade 1-3*	*MIC Grade 1*	*MIC Grade 2*	*MIC Grade 3*	*MAC Grade 1*	*MAC Grade 2*	*MAC Grade 3*
1-33	0	0.07 (0–0.21)	0.18 (0–0.41)	0	0.11 (0–0.32)	0.21 (0.03–0.39)	0.67 (0.13–100)
34-66	0	0.06 (0–0.17)	0.04 (0–0.13)	0.21 (0–0.43)	0.10 (0–0.22)	0.36 (0.18–0.53)	0.47 (0.21–0.72)
67-100	0	0.15 (0.03–0.27)	0.16 (0.05–0.27)	0.07 (0–0.21)	0.34 (0.21–0.47)	0.36 (0.27–0.45)	0.61 (0.47–0.74)

Values in parentheses represent 95% confidence intervals. ITC: isolated tumor cells; MIC: micrometastasis; MAC: macrometastasis

weight. Indeed, most of the series finding tumor size as a significant predictor of non-SLN involvement used this parameter as reflected by the relatively large scales of the pT categories, and included tumors belonging in the pT2 and pT3 sizes.

Conclusion

In summary, on the basis of the results derived from this multi-institutional cohort, it seems that SLNB (similarly to any other axillary surgical staging procedure) can be omitted for DCIS, but should be considered the general staging procedure even for small breast carcinomas. The exceptions to this rule may be small invasive (up to 2-4 mm, or up to 10 mm in case of a low grade and unifocality) carcinomas. Whenever an SLN is found to be positive, the generally indicated axillary dissection (or radiotherapy, which is considered as a potentially suitable alternative to dissection from the therapeutic point of view) can be avoided in cases of DCIS, SLN involvement by ITCs, and probably in small tumors up to 4 mm, or well-differentiated tumors with an SLN ratio below 0.67. The potential risks and benefits must be discussed with the patients, as even higher risks of estimated non-SLN involvement may be acceptable under some circumstances.

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