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Clinical trial

Patients with preoperatively ultrasonically uninvolved axillary lymph nodes: a distinct subgroup of early breast cancer patients

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Summary

Introduction. Ultrasound (US) preoperative examination of the axillary lymph nodes combined with the fine needle aspiration biopsy (FNAB) is often used in order to reduce the number of sentinel lymph node (SLN) biopsy procedures in clinically node negative breast cancer patients. The pathohistological characteristics of the ultrasonically negative axillary lymph nodes in clinically negative axillary lymph nodes are not known. The aim of our study was to compare the pathohistological characteristics of ultrasonically uninvolved axillary lymph nodes (US group) versus clinically uninvolved axillary lymph nodes (non-US group) in SLN biopsy candidates.

Methods. We included 658 patients after SLN biopsy; 286 patients in the US group and 372 in the non-US group. The pathohistological characteristics of axillary lymph nodes were evaluated by univariate analysis and logistic regression.

Results. In the univariate analysis, the proportion of macrometastastic SLN, total number of metastatic lymph nodes per patient, proportion of nonsentinel lymph node (NSLN) metastases and proportion of NSLN macrometastases were found to be lower in the US group compared to the non-US group. In the logistic regression model, only US of the axilla ($p = 0.010$; OR: 0.57) and tumor size were significant predictors for the presence of SLN macrometastases or macrometastatic NSLN ($p < 0.001$; OR: 0.23).

Conclusion. The patients with US negative axillary lymph nodes form a distinct subgroup of early breast cancer patients having a significantly lower tumor burden in the axillary lymph nodes compared to those with only clinically negative axillary lymph nodes.

Introduction

Sentinel lymph node (SLN) biopsy has become an accepted alternative to routine axillary lymph node dissection (ALND) in clinically node negative early breast cancer patient [1]. ALND can safely be omitted in SLN negative breast cancer patients, as shown by recent data [2–4]. Thus, the patients with pathohistologically uninvolved SLN can be spared ALND and its sequels. In contrast, in the patients with pathohistologically metastatic SLN, ALND is routinely performed due to high risk (up to 79%) of non-sentinel lymph nodes (NSLN) metastases [5].

However, the SLN biopsy procedure has several pitfalls. It is costly, time consuming and it often results in a second operation if the SLN metastases were not detected intraoperatively. In order to reduce the number of SLN biopsy procedures, efforts were made to improve the staging of the axillary lymph nodes by using imaging techniques either alone [6–8] or combined with fine needle aspiration biopsy (FNAB) [9–12]. It was reported that the preoperative US-guided FNAB of the axillary lymph nodes revealed metastases in the axillary lymph nodes in 10–20% of the SLN biopsy candidates; these patients proceed directly to ALND [9–12]. The remaining patients with ultrasonically uninvolved axillary lymph nodes (or ultrasonically suspicious lymph nodes, but not confirmed by the FNAB) proceed to the SLN biopsy.

Until now, the impact of the US-guided FNAB selection of the metastatic axillary lymph nodes on the pathohistological characteristics of the axillary lymph nodes in clinically node negative has not been known. According to our hypothesis, the axillary tumor burden

is significantly lower in the patients with ultrasonically uninvolved axillary lymph nodes. The aim of our study was to compare the histopathological characteristics of axillary lymph nodes of the patients with clinically uninvolved axillary lymph nodes and of those with ultrasonically uninvolved axillary lymph nodes.

Patients and methods

Patients

From January 2000 to September 2004, the sentinel lymph node biopsy was successfully performed as a routine procedure in 705 unifocal invasive breast cancer patients at the Institute of Oncology Ljubljana. Clinical examination of the breasts and the bilateral regional axillary and supraclavicular lymph nodes were performed by surgeons who operated on the patients. All patients had clinically negative axillary lymph nodes.

The preoperative US of the axilla was performed in 382 SLN biopsy candidates. In 49 of these patients, the US-guided FNAB of the axillary lymph nodes revealed metastases in the lymph nodes. These patients proceeded directly to ALND. In the remaining 333 patients, the SLN biopsy was performed. From these patients, we additionally excluded from the study,

(i) 41 patients with US suspicious lymph nodes,

(ii) 6 patients with false negative SLN; in 2 of these patients, the intramammary lymph node contained metastases, and in 4 patients, the additionally removed clinically suspicious lymph nodes contained metastases.

In 372 patients who underwent SLN biopsy, the preoperative US of the axilla was not performed.

In the present retrospective study, altogether 658 patients were included:

(1) US group (286 patients): Clinically negative axillary lymph nodes. The preoperative US examination of the axillary lymph nodes performed, showing no axillary pathology.
(2) Non-US group (372 patients): Clinically negative axillary lymph nodes.

The clinicopathological data of the patients are shown in Table 1.

The informed consent for the SLN biopsy procedure was signed by all patients.

Preoperative ultrasound procedure

The preoperative US examination of the axilla was performed as described in detail elsewhere [12]. Briefly, ultrasound examination of the axilla was performed by experienced radiologists, using a linear-array transducer with range 12–15 MHz (Power Vision 8000 model SSA-390A; Toshiba, Otawara, Japan).

Table 1. Clinicopathological characteristics of patients and tumors

		US group	Non-US group
No. patients		286	372
Tp (mm)*	T1a	6 (2%)	27 (7%)
	T1b	59 (21%)	95 (26%)
	T1c	141 (49%)	184 (49%)
	T2	79 (28%)	64 (17%)
	T3	1 (0%)	2 (0%)
Age	range	28–80	23–80
	Mean	57.1	56.8
	Median	53.6	56
Tumor type	IDC**	254 (89%)	319 (86%)
	ILC***	28 (10%)	45 (12%)
	other	4 (1%)	8 (2%)
Grade	1	113 (30%)	80 (28%)
	2	168 (45%)	127 (44%)
	3	84 (23%)	77 (27%)
	unknown	7 (2%)	2 (1%)
ER+/PR+****		266 (72%)	216 (76%)
ER+/PR−		42 (11%)	30 (10%)
ER−/PR+		10 (3%)	4 (1%)
ER−/PR−		54 (14%)	36 (13%)

* Histopathological tumor size.
** Invasive Ductal Carcinoma.
*** Invasive Lobular Carcinoma.
**** Estrogen receptor status positive (=>10%).
**** Progesteron receptor status positive (=>10%).

In each Us visible lymph node the longitudinal and the transverse axis dimensions were measured in order to obtain longitudinal-transverse axis ratio (L/T). The presence or absence of central echogenic hilus was documented. If central echogenic hilus was detected, than the maximum cortex thickness of the LN was measured.

For each visible lymph node, color Doppler interrogation was performed and the distribution of vessels was defined as hilar-central (benign) and non-hilar-peripheral or mixed (malignant) vessel signals.

Lymph node was suggestive of metastatic involvement if one of the following criteria were met: the L/T ratio ≤ 1.2, lymph node hilus not seen or the cortex thickness larger than 3 mm; in these lymph nodes an US-FNAB with a 21-G needle was performed and two smears were prepared. Based on our ROC analysis the L/T index was the most powerfull predictor of Lymph node metastases [12].

Sentinel lymph node procedure

For the lymphatic mapping, 30–60 MBq of 99m Tc labelled nanocolloid (Nanocol) in 0.2 ml saline, divided in two doses, injected peritumorally at two sites, was used. After obtaining the dynamic and static lymphoscintigraphy and marking the SLN on the skin, 1 ml of Patent blue (Blue Patente V; Laboratorie Guerbet, Aulnaysous-Bois, France) was injected peritumorally only few minutes prior to the surgery. The SLN

dissection was guided by a hand-held gamma probe (Navigator GPS System, USSC, Watertown, Massachusetts, USA) and/or by the blue stained afferent lymphatic channel. The excised SLNs were measured for *ex-vivo* radioactivity; hot lymph nodes with the radioactive count ratio of the background radioactivity to the hottest *ex-vivo* SLN of more than 1/10 were also removed [13]. Additionally, if clinically suspicious non-hot non-blue lymph nodes were encountered, they were removed and signed separately. For the purpose of the present study, these additionally removed lymph nodes were counted as sentinel nodes.

For the intraoperative examination of SLNs, the touch imprint cytology (TIC) was used, as described elsewhere [13]. If the TIC was positive, immediate ALND was performed.

All slices of SLNs were than formalin-fixed and embedded in paraffin. The slides were examined with H&E staining. For all negative SLNs, serial sections were evaluated with H&E and cytokeratin immunohistochemistry (IHC) stained levels at 250 μm. IHC staining was performed using avidin-biotin-peroxidase complex method with commercially obtained monoclonal anti-cytokeratin antibody, clone MNF 116 (Dako, Glostrup, Denmark).

According to the TNM staging system [14], the metastatic deposits with the size ranging between 0.2 and 2 mm were considered as micrometastases, and those with the size less than 0.2 mm, as isolated tumor cells (ITC).

All NSLNs were sectioned transversely at 2–3 mm and entirely embedded. One section was examined with one H&E staining per paraffin block.

Statistical analysis

For univariate statistical analysis, *t*-test, Mann-Whitney Rank Sum test and contingency tables were used. For multivariate analysis, logistic regression was used.

Results

Altogether, 1405 sentinel lymph nodes were removed (mean 2.1/patient, SD 1.3, range 1–11). Of these, 84 lymph nodes were removed in 60 patients as "additional clinically suspicious lymph nodes". The results of lymph node biopsy for the two groups are summarized in Table 2.

Table 2. Univariate analysis of the histopathological results between the US and non-US group

		US group	Non-US group	*p*-value
No. patients		286	372	
Tp (mm)*		mean 17, median 16	mean 14.5, median 14	<0.001
Number of SLN removed per patient		Mean 2.2, median 2	Mean 2.1, median 2	NS
SLN positive patients		114/286 (40%)	144/372 (39%)	NS
Number of positive SLN per patient		Mean 1.2, median 1	Mean 1.2, median 1	NS
		SD 0.58	SD 0.49	
SLN metastases size	*macromet.*	42/114 (37%)	76/144 (53%)	0.029
	micromet.	50/114 (44%)	43/144 (30%)	
	*ITC***	22/114 (19%)	25/144 (17%)	
Proportion of positive	*0%*	172 (60.1%)	228 (61.3%)	NS
SLN per patient***	*>0% and <100%*	60 (21.0%)	67 (18.0%)	
	100%	54 (18.9%)	77 (20.7%)	
LVI**** of the primary tumor (SLN positive only)		28/114 (25%)	40/144 (28%)	NS
ALND***** following positive SLN	*Number of ALND performed*	79/114 (69%)	96/144 (67%)	NS
	Total number of lymph nodes removed	range 6–34	range 7–37	NS
		mean 18.5	mean 19.3	
		median 19	median 18	
	Total number of positive lymph nodes	range 1–9	range 1–28	0.003
		mean 1.7	mean 3.2	
		median 1	median 2	
NSLN****** metastases	*NSLN positive*	18/79 (23%)	43/96 (45%)	<0.001
	NSLN macromet.	12/18 (67%)	40/43 (93%)	0.015

* Histopathological tumor size.
** Isolated tumor cells.
*** Number of positive SLN per patient /total number of SLN removed per patient.
**** Lymphovascular invasion.
***** Axillary lymph node dissection.
****** Nonsentinel Lymph Node.

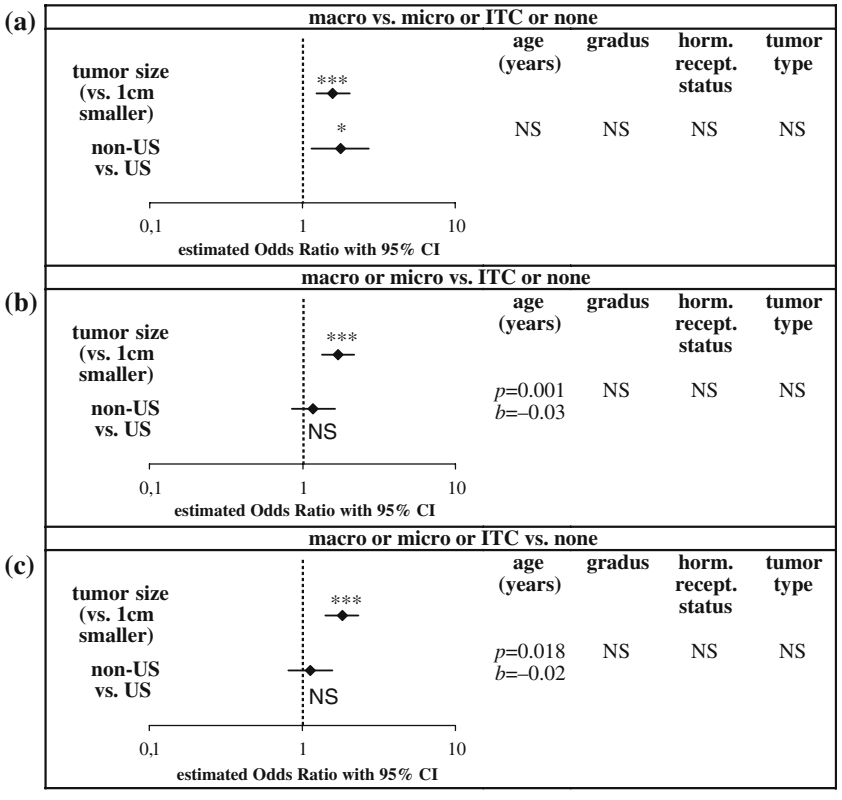
Three regression models were fitted for predicting the presence of metastases in the axillary lymph nodes from US of the axilla (negative versus not performed), controlling for age, tumor size, gradus, hormonal receptor status (ER or PR 10 or more), and tumor type (Figure 1 a–c). When predicting macrometastases versus multiple micrometastases, micrometastases, ITC or none, the model was statistically significant ($p = 0.001$), and for the patients with negative US nodes, the probability of finding macrometastases was significantly lower than for the patients who did not undergo US ($p = 0.010$; estimated odds ratio (OR) 0.57, 95% confidence interval (CI) 0.37–0.87), while the only other statistically significant predictor was tumor size (odds for finding macro metastases increase with tumor size) (Figure 1a). When predicting macro-, or micro-metastases versus ITC or none, the model was statistically significant ($p < 0.001$); the estimated influence of US was in the expected range (estimated lower odds for the US group) but not statistically significant ($p = 0.372$), while the statistically significant predictors were age (lower odds with increasing age) and tumor size (higher odds with larger tumor size) (Figure 1b). The same results were obtained when predicting the presence of any kind of metastases (macrometastases, micrometastases, ITC) versus. none ($p = 0.497$ for US) (Figure 1c).

Two regression models were fitted for predicting positive NSLNs in the patients, who underwent ALND, from US of the axilla (negative versus not performed), controlling for age, tumor size, gradus, hormonal receptor status, tumor type, proportion of positive SLNs (none, above 0% and below 100%, all) of the SLNs removed, and lymphovascular invasion (LVI) (Figure 2 a–b). When predicting the presence of macrometastases versus micrometastases or none, the model was statistically significant ($p = 0.003$), and for the patients with negative US, the probability of finding macrometastases in NSLNs was significantly lower than of the patients who did not undergo US ($p < 0.001$; estimated OR 0.23, 95% CI: 0.10–0.52), while the only other statistically significant predictor was tumor size (odds for finding NSLN with macrometastases increase with tumor size) (Figure 2a). Equivalent results were obtained when predicting the presence of either macro- or micrometastases versus none in NSLNs (model: $p = 0.007$; US: $p = 0.005$, estimated odds OR 0.35, 95% CI: 0.17–0.73) (Figure 2b).

Discussion

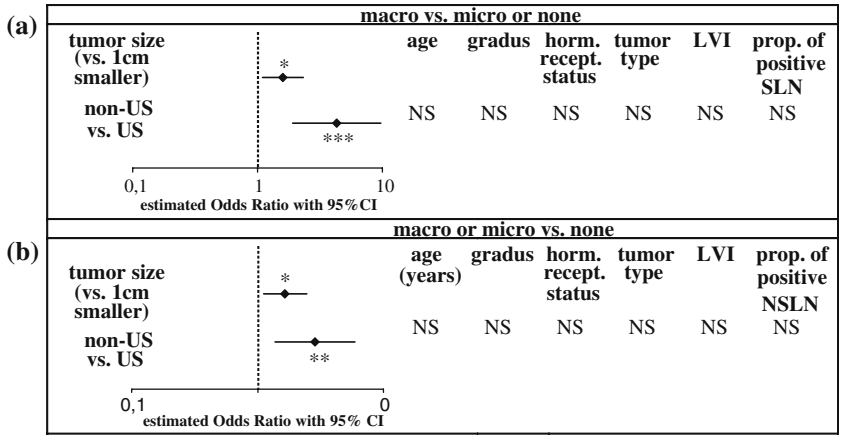
The inaccuracy of the clinical examination in determining the axillary lymph node status has been long known [15, 16] with the overall accuracy ranging from 63 to 66% [17, 18]. Small metastases cannot be palpated which is particularly difficult in obese patients. Furthermore, clinical examination can be false positive, due to nonmalignant adenopathy or simply due to normal variation of lymph node size and fat content [19].

It has been therefore assumed that an additional patients selection by using the US examination of the



(*** $p<0.001$; ** $p<0.01$; * $p<0.05$)

Figure 1. Summary of regression analyses for the prediction of SLN metastases.



(*** $p<0.001$; ** $p<0.01$; * $p<0.05$)

Figure 2. Summary of regression analyses for the prediction of NSLN metastases.

clinically negative axillary lymph nodes (combined with FNAB) should have an impact on the patohistological characteristics of the axillary lymph nodes. Indeed, the present study clearly shows that the US-negative axillary lymph node group of patients form a distinct subgroup of early breast cancer patients. Namely, when US-negative axillary lymph nodes were compared to clinically negative axillary lymph nodes, we found a statistically significant lower axillary lymph nodes tumor burden in the US group. When we studied our results in details we observed:

(i) Lower proportion of patients with macrometastatic SLNs in the US group.This finding is not surprising as the ultrasound resolution allows the detection of macrometastases but not of micrometastases and/or ITC. Indeed, the proportion of micrometastases and ITC in SLNs was not significantly different between the groups in our study. In the logistic regression model, the only two predictors of the macrometastatic involvement of the SLN were US, followed by tumor size (Figure 1a). When fitting the logistic regression model for the lymph node metastases according to the current TNM system (Figure 1b) or for any lymph node involvement (Figure 1c), US was not a statistically significant predictor of the SLN metastases. Surprisingly, however, in these two models (Figure 1b, c), beside the primary tumor size, the age appeared as a significant predictor of the SLN positivity; our data suggest that the probability of small SLN metastases (micro and ITC) is higher in younger patients. This is in contrast to the studies published so far (reviewed in [5]). This finding can be a consequence of the inclusion of US in the multivariate model, which has not been done until now.

(ii) Lower total number of metastatic lymph nodes per patient in the US group of patients with ALND performed in comparison to the non-US group of ALND patients. This difference was significant although both groups were well matched regarding the average number of SLNs removed per patient, the average number of metastatic SLN per patient, and the SLN ratio of SLN positivity (Table 2). This finding can be explained by the lower proportion of the patients with macrometastatic SLNs in the US group. Namely, the size of the SLN metastases was consistently shown in numerous studies to be a significant predictor of the NSLN metastases [5, 20–22]. Hence, due to lower proportion of patients with macrometastastic SLNs in the US group, also the total number of metastatic lymph nodes per patient is lower.

(iii) Lower number of patients with metastatic NSLN in the US group. As expected, the difference was observed particularly in the number of patients with macrometastatic NSLN, due to the ability of US to detect macrometastases. Surprisingly, LVI and the proportion of positive SLNs in our series were not predictors of the NSLN metastases. This is in contrast to published evidence that included the LVI [22–24] or the proportion of positive SLNs [21] as predictors of the NSLN metastases. As shown by our results, only US and tumor size were significant predictors of the NSLN metastases.

Our findings might have several implications:

1. The reduced probability of NSLN metastases, as shown by our results, might change the regional treatment choice. Controversy arises over the most appropriate regional treatment of SLN positive patients and this question is currently being addressed by several randomized trials (ACOSOG Z 11, AMAROS, IBCSG 23). Namely, approximately 50 % of SLN positive patients harbor metastases also in the NSLN axillary lymph nodes in most series [5]. Although randomized trials failed to show an advantage of elective ALND in clinically node negative patients [25], there is concern that the residual regional tumor burden might be associated with worse prognosis [26]. In our study, the risk of NSLNs was significantly lower in the US group; particularly the risk of macrometastases, being 15%

in the US group compared to 43% in the non US group.

2. Numerous studies tried to determine factors related to NSLN metastases in SLN positive patients [5, 21–22, 27–29]. However, in none of these studies, a subgroup of patients with an acceptably low risk of NSLN metastases could be determined. The best prediction model of the NSLN metastases presented so far was the MSKCC Nomogram [20]. We suggest to improve further the Nomogram by adding the preoperative US of the axilla as one of the factors to calculate the NSLN risk. Namely, the probability of NSLN metastases was significantly reduced in our study in the US-negative group of patients.
3. Preoperative US should be considered as a stratification criteria in randomized trials. As mentioned above, several randomized trials are currently enrolling patients to compare different regional therapies in the SLN positive patients: EORTC AMAROS trial is comparing ALND versus radiotherapy, IBCSG 23 ALND versus observation in micrometastatic SLN, and ACOSOG Z11 ALND versus observation. In none of these studies, however, the preoperative US of the axilla is a stratification factor at randomization, although we can assume that, at least in some collaborating centers, the preoperative axillary US is routinely performed. In our study, 23% of patients in the US group had additional NSLN metastases, one third of them were micrometastatic. Thus, in the majority (77%) of patients with negative US of the axilla, NSLNs are free of metastases. If these patients were randomized in a study, they would not add to the power of the study. This situation is similar to the past malignant melanoma studies, comparing the elective lymph node dissection to observation: as only 20% of randomized melanoma patients had lymph node metastases, some studies showed a survival advantage of the elective lymph node dissection only after 10 years [30].
4. We observed a trend towards a lower proportion of patients with positive SLN in the US group, although it was not statistically different (Figure 1b, c). A lower proportion of SLN positive patients should increase the NPV (negative predictive value) of the SLN biopsy procedure. The NPV is defined as NPV = True Negative (TN)/(TN + False negative (FN)). Namely, by reducing the True Positive (TP), FN is decreased, which decreases the NPV denominator; hence, NPV can be increased. Therefore, the accuracy (Accuracy = (TP + TN)/total cases) of the SLN biopsy could be further improved by the preoperative US examination of the axilla.

As shown by our data, 49/382 patients (13%), in whom US was preoperatively performed, did not proceed to the SLN biopsy because of the US/FNAB proven axillary metastases. This is considerably less when compared to 19% in our recently reported prospective study [12]. We can explain the difference by more thorough US examinations of the axilla in the reported study that were performed by few dedicated radiologists [12], while the present series includes also the patients that did not take part in the above mentioned study.

The patients with the lymph nodes found suspicious for the metastases by the preoperative US, but not confirmed by FNAB, were not included in the present study. The number of these patients was too low (41) to allow us a detailed statistical analysis of this subgroup of patients. As expected, the proportion of SLN positive patients was high in this subgroup of patients (26/41), most of them had macrometastastic SLNs (15/26). This subgroup of patients needs to be further evaluated with a larger number of patients included.

Our study has several pitfalls; it is a nonselected, non-randomized observational study. The inclusion of patients in either of the groups was prone to selection bias. This is best seen in the difference of the average tumor size between the groups. There are two reasons for that. First, when the SLN biopsy was introduced to our institution, we were more likely to select patients with small tumors for the procedure. The US of the axilla was introduced later on, when also patients with larger tumors were routinely offered SLN biopsy. Second, the surgeons more likely asked to perform the axillary US in the patients with larger breast tumors. However, despite these pitfalls, multivariate analysis enabled us to draw reliable conclusions out of the study.

Conclusion

Our study showed that the patients with ultrasonically uninvolved axillary lymph nodes form a distinct subgroup of early breast cancer patients. Preoperative axillary US examination should be recommended in candidates for SLN biopsy. Furthermore, it might be considered as one of the stratification criteria when designing clinical trials.

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