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ORIGINAL ARTICLE – BREAST ONCOLOGY

The Role of Ultrasound-Guided Lymph Node Biopsy in Axillary Staging of Invasive Breast Cancer in the Post-ACOSOG Z0011 Trial Era

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ABSTRACT

Background. Axillary status in invasive breast cancer, established by sentinel lymph node biopsy (SLNB) or ultrasound-guided lymph node biopsy, is an important prognostic indicator. The ACOSOG Z0011 trial showed that axillary dissection may be redundant in selected sentinel node-positive patients, raising questions on the applicability of these conclusions on ultrasound positive patients. The purpose of this study was to evaluate potential differences in patient and tumor characteristics and survival between axillary node positive patients after ultrasound (US group) or sentinel lymph node procedure (SN group).

Methods. Patients diagnosed with invasive breast cancer at the Máxima Medical Center between January 2006 and December 2011 were studied.

Results. In total, 302 node-positive cases were included: 139 and 163 cases in the US and SN groups, respectively. Patients in the US group were older at diagnosis ($p < 0.001$), more often had palpable nodes ($p < 0.001$), mastectomy ($p < 0.001$), larger tumors ($p < 0.001$), higher tumor grade ($p = 0.001$), lymphovascular invasion ($p = 0.035$), a positive Her2Neu ($p = 0.006$), and a negative hormonal receptor status ($p = 0.003$). Also, they were more likely to have more lymph nodes with macrometastases ($p < 0.001$), extranodal extension ($p < 0.001$), and involvement of level-III-lymph node ($p < 0.001$). Finally, they showed a worse disease-free survival [hazard ratio (HR) = 2.71; 95 % confidence interval (CI) = 1.49–4.92] and overall survival (HR = 2.67; 95 % CI = 1.48–4.84) than the SN group.

Conclusions. These results suggest that ultrasound-positive patients have less favorable disease characteristics and a worse prognosis than SN-positive patients. Therefore, we conclude that omitting an ALND is as yet only applicable, as concluded in the Z0011, in patients with a positive SLNB.

Axillary lymph node status in patients with invasive breast cancer is still an important prognostic indicator. It can be determined by ultrasound-guided lymph node biopsy (UGLNB) or sentinel lymph node biopsy (SLNB).[1,2] There are differences in European versus American guidelines concerning the axillary workup.[3–5] Current American guidelines dictate to perform the UGLNB only in patients with palpable lymphadenopathy, although clinical palpation has a false-negative rate of 30–50 %.[6,7] In European guidelines, however, the axillary ultrasound is a routine element in all breast cancer patients with or without palpable lymph nodes.[3,4]

Multiple studies have shown that in 40–70 % of sentinel node positive patients additional lymph nodes do not contain any metastases.[8–11] The ACOSOG Z0011 trial showed that an axillary lymph node dissection (ALND) may be safely omitted in selected patients with a positive SLNB.[12] However, questions are raised whether these criteria can be applied to patients with a positive UGLNB. This may be the case if no clinically relevant differences

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are present in tumor and/or patient characteristics or survival between both groups. If differences exist, however, this could mean that a distinction has to be made in the management of the axilla between patients with a positive UGLNB versus those with a positive SLNB.

Hence, the purpose of this study was to evaluate potential differences in patient, tumor, and lymph node characteristics and outcome between patients with a positive UGLNB and patients with a positive SLNB.

PATIENTS AND METHODS

This study included patients diagnosed with primary invasive breast cancer between January 2006 and December 2011 at the Máxima Medical Center. Data were retrieved from the population-based Eindhoven Cancer Registry and medical charts of patients. In accordance with Dutch guidelines, after mammography and clinical evaluation all patients were referred to the radiologist for sonographic evaluation of the breast tumor and ipsilateral axilla. Ultrasound-guided lymph node biopsies were performed on the tumor and on suspicious axillary lymph nodes. If pathological analysis showed that the biopsy was negative or inconclusive, patients underwent a SLNB. Patients were included if they had cytologically or histologically proven axillary lymph node metastases after either an UGLNB or a SLNB. Patients with stage IV breast cancer, those treated within the neoadjuvant setting, patients with a clinical N_2 or N_3 axillary nodal status, or patients who did not undergo an ALND were excluded. Patients with bilateral carcinoma were considered as separate observations.

Ultrasound-guided Lymph Node Biopsy

Licensed radiologists performed the UGLNB using a Toshiba Aplio XG machine for sonographic evaluation. A green 21- or blue 23-gauge needle was used for cytological samples of the axillary lymph node and, on indication, a 14- or 18-gauge needle to obtain histological samples, after injecting approximately 10 cc of lidocaine-1 % for local anesthesia. The lymph nodes were evaluated with respect to following characteristics: diffuse or focal cortical enlargement, loss of lymph node fatty hilum, and nodal size (long and short axis).[3,13,14] In case of multiple morphologically abnormal axillary lymph nodes, the largest or most malignant imposing lymph node was biopsied. Cytological samples of the lymph node were stained with a Papanicolaou stain and with a Giemsa-stain for cytological analysis. Histological analysis was performed by hematoxylin and eosin (H&E) staining and immunohistochemistry.

Sentinel Lymph Node Biopsy

Analysis of the sentinel lymph node was performed with a combined colorimetric-radioisotope method. This procedure has been extensively illustrated in previous publications.[15,16] The sentinel lymph nodes were analyzed by routine histopathological analysis (H&E-staining and immunohistochemistry).

Data Analyses

Clinical data included in the analysis were age, body mass index, year of diagnosis, lateralization of the tumor, clinical palpability of the axillary lymph nodes, and type of surgery (mastectomy or breast conserving). Histopathological data collected on the tumor included tumor size in millimeters, tumor type, tumor grade using the Nottingham-modification-scale, lymphovascular invasion, Her2Neu status, and the presence of estrogen or progesterone receptors. Estrogen and progesterone receptor status were considered positive if 10 % or more of the material contained the appropriate receptors. The variable multifocality also was included in the analysis and was defined as tumors occurring in multiple sites in the breast. Due to lacking data in the pathological reports, it was not possible to make a clear distinction between multifocality and multicentricity. Histopathological data on both the sentinel and axillary lymph nodes included total number of resected lymph nodes, total number of positive nodes, size of largest metastases in the sentinel lymph node, divided in macrometastases (>2 mm) or (sub)micrometastases ($\leq$2 mm), extranodal extension, and involvement of the level-III-axillary lymph node. The total number of resected lymph nodes was computed by adding the total number of resected lymph nodes during ALND to the number of resected lymph nodes during the SLNB. The total number of positive axillary lymph nodes was categorized as minimal nodal involvement ($\leq$2 positive nodes) or extensive nodal involvement ($\geq$3 positive lymph nodes), as proposed by the Z0011 trial.

Chi square analyses or a Fisher's exact test were used to assess differences in patient and tumor characteristics between the ultrasound group and the sentinel node group. A p value of $\leq$0.05 was considered statistically significant. Survival and disease-free survival analyses were conducted using the life-table method, the Kaplan–Meier Curve, and Cox regression analysis. Disease-free survival was calculated from date of diagnosis until date of occurrence or metastases and/or locoregional relapse. Overall survival was calculated from date of diagnosis until death or last documentation. Follow-up was updated until April 2014. Loss of follow-up was defined as death or lack of documentation on health status for more than 1 year, without

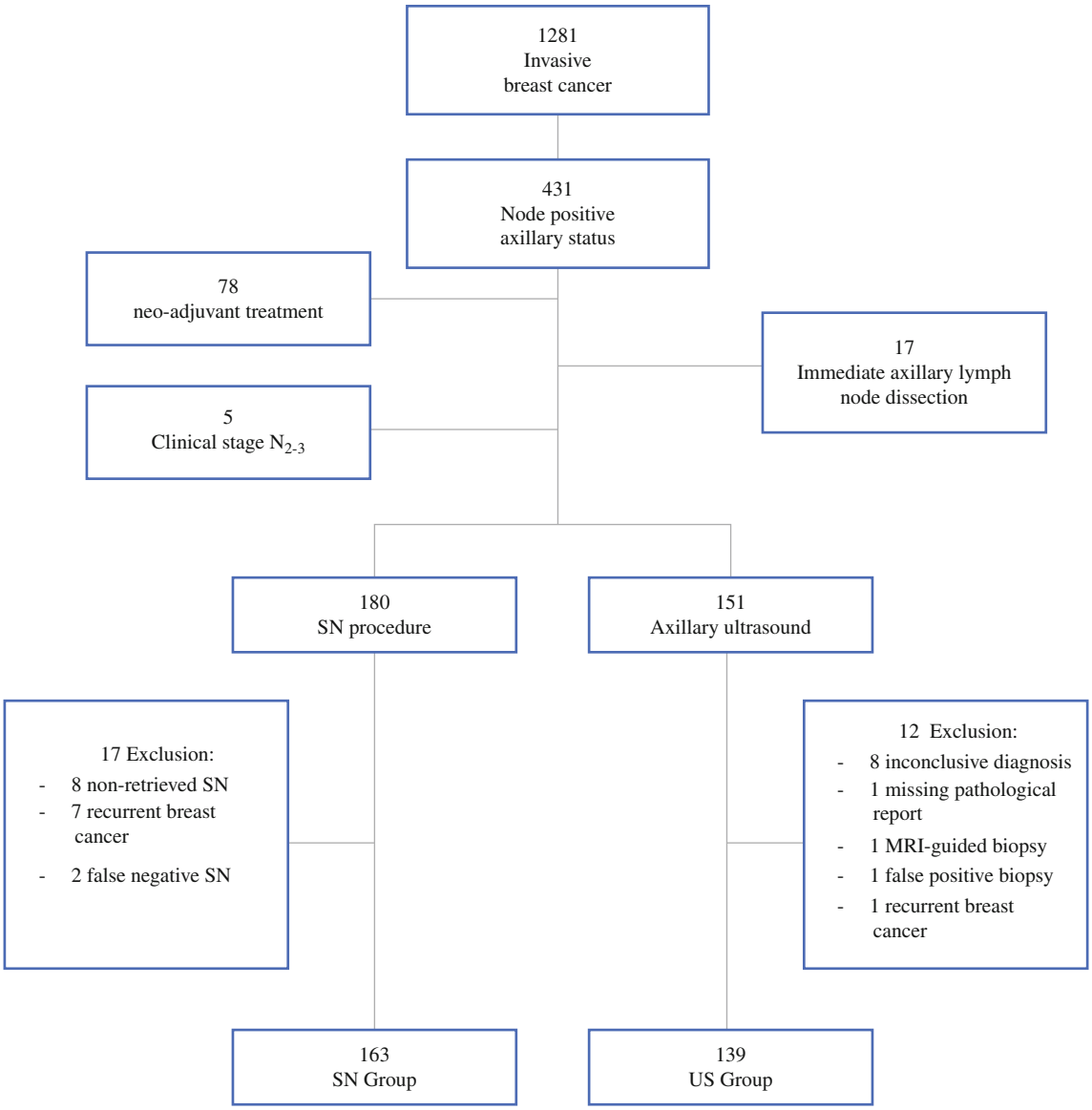

FIG. 1 Flowchart of patient selection showing the inclusion of 163 cases in the sentinel node group and 139 cases in the ultrasound group. SN group = sentinel node-positive patients; US group = patients with a positive ultrasound-guided lymph node biopsy

having a new appointment in the near future at the breast center. Thirteen patients were considered lost to follow-up.

RESULTS

From January 2006 until December 2011, 1,281 cases of invasive breast cancer without metastatic disease were treated. In 431 (33.6 %) cases axillary metastases were found. Of these, 78 cases receiving neoadjuvant systemic therapy, 5 cases with clinical nodal status $N_{2–3}$ and 17 cases which immediately underwent an ALND without a previous axillary biopsy were excluded. Of the remaining 331 cases, 151 had a positive axillary ultrasound (US group), whereas 180 cases had a positive sentinel node (SN group). Subsequently, another 29 cases were excluded for various reasons listed in Fig. 1.

Hence, a total of 302 cases, representing 301 patients, were analysed including 139 cases in the US group and 163 cases, equalling 162 patients, in the SN group. The median age was 60 years; all patients, except one in the SN group, were female.

Univariate Analyses on Differences in Characteristics

Patients in the US group were older and more likely to have palpable lymphadenopathy than those in the SN group. Patients in the US group also had larger tumors with a higher tumor grade and more patients had a negative

TABLE 1 Univariate analysis of patient and tumor characteristics showing significant differences between axillary node positive patients identified by ultrasound versus sentinel node biopsy

Patient characteristics	Ultrasound		Sentinel node		*p* value
	(*n* = 139)		(*n* = 163)		
Age					<0.001
Median [range]	64	[23–89]	57	[27–89]	
<50 year	38	(27.3 %)	38	(23.3 %)	
50–69 year	48	(34.5 %)	92	(56.4 %)	
≥70 year	53	(38.1 %)	33	(20.2 %)	
BMI					0.859
Normal weight	62	(43.4 %)	68	(41.5 %)	
Overweight	49	(35.3 %)	62	(38.0 %)	
(Morbid) obesity	28	(20.2 %)	33	(20.2 %)	
Year of diagnosis					0.290
2006–2008	75	(54.0 %)	78	(47.9 %)	
2009–2011	64	(46.0 %)	85	(52.1 %)	
Palpability of axillary nodes					<0.001
No	54	(38.8 %)	130	(79.8 %)	
Yes	82	(61.2 %)	18	(11.0 %)	
Unknown	3	(2.2 %)	15	(9.2 %)	
Side of tumor					0.367
Right	61	(43.9 %)	80	(49.1 %)	
Left	78	(56.1 %)	83	(50.9 %)	
Type of surgery					<0.001
Breast conserving	49	(35.3 %)	112	(68.7 %)	
Mastectomy	90	(64.7 %)	51	(31.3 %)	
Tumor size in mm					<0.001
Median [range]	25	[5–79]	18	[2–76]	
<20 mm	23	(16.5 %)	95	(58.3 %)	
20–30 mm	64	(46.0 %)	49	(30.1 %)	
>30 mm	52	(37.0 %)	19	(11.7 %)	
Morphology of tumor					0.635
Ductal carcinoma	108	(77.7 %)	122	(74.8 %)	
Lobular carcinoma	23	(16.5 %)	27	(16.6 %)	
Other types	8	(5.8 %)	14	(8.6 %)	
Tumor grade					0.001
Grade 1	23	(16.5 %)	58	(35.6 %)	
Grade 2	75	(54.0 %)	74	(45.4 %)	
Grade 3	38	(27.3 %)	30	(18.4 %)	
Unknown	3	(2.2 %)	1	(0.6 %)	
ER status					<0.001
Negative	39	(28.1 %)	17	(10.4 %)	
Positive	100	(71.9 %)	146	(89.6 %)	
PR status					0.001
Negative	59	(42.4 %)	41	(25.2 %)	
Positive	80	(57.6 %)	122	(74.8 %)	
Her2Neu status					0.006
Negative	113	(81.3 %)	149	(91.4 %)	
Positive	26	(18.7 %)	13	(8.0 %)	
Unknown	0	(0 %)	1	(0.6 %)	
Triple negative					0.080
No	117	(84.2 %)	148	(90.8 %)	
Yes	22	(15.8 %)	15	(9.2 %)	
Multifocality					0.087
No	111	(79.8 %)	119	(73.0 %)	
Yes	24	(17.3 %)	42	(25.8 %)	
Unknown	4	(2.9 %)	2	(1.2 %)	
Lymphovascular invasion					0.035
No	80	(57.5 %)	118	(72.4 %)	
Yes	34	(24.5 %)	27	(16.6 %)	
Unknown	25	(18.0 %)	18	(11.0 %)	

ER estrogen receptor, *PR* progesterone receptor

estrogen and/or progesterone receptor status (38 vs. 10 %, respectively) and a positive Her2Neu receptor status (Table 1). Furthermore, in the US group, the number of lymph nodes removed from the axilla was higher, as were the number of positive lymph nodes with macrometastases, the risk of extranodal extension and level-III lymph node metastases compared to the SN group (Table 2). Multifocality and a triple negative receptor status were borderline not significantly different between the groups. When selecting only patients without palpable lymphadenopathy, a total of 184 cases, all differences presented in Tables 1 and 2, except for Her2Neu receptor status, progesterone receptor status and the presence of lymphovascular invasion, remained statistically significant. In addition, a significant difference in the proportion of patients with triple negative disease was observed ($p = 0.043$) between the US versus the SN group.

Survival Analysis

The median follow-up time was 4 years. During follow-up, a total of 54 patients (18 %) died of whom 33 (61 %) as a result of breast cancer and 12 (22 %) due to unrelated causes. In nine patients, the cause of death was unknown. Locoregional relapse, solely or before the occurrence of metastases, occurred in seven patients: five patients (three in US group and two in SN group) had a local recurrence in the breast and two patients had a regional relapse (one in both groups).

In the US group, 33 patients suffered from distant metastases and/or locoregional relapse compared to 16 patients with a positive SLNB. Survival analysis on the included patients showed a 5-year disease-free survival of 72.6 % (95 % CI, 71.8–73.4) in the US group versus 87.7 % (95 % CI, 87.2–88.2) in the SN group

TABLE 2 Univariate analysis of characteristics of axillary lymph nodes showing significant differences between axillary node positive patients identified by ultrasound versus sentinel node biopsy

Axillary lymph nodes	Ultrasound		Sentinel node		p value
	(n = 139)		(n = 163)		
Lymph nodes removed					0.001
Median [range]	15	[3–41]	13	[3–27]	
Total positive lymph nodes					<0.001
Median [range]	4	[1–41]	1	[1–16]	
1–2 nodes	51	(36.7 %)	126	(77.3 %)	
3 or more nodes	88	(63.3 %)	37	(22.7 %)	
Size of axillary metastasis					0.000
Macro	126	(90.5 %)	109	(66.9 %)	
Micro	4	(2.9 %)	54	(33.1 %)	
Unknown	9	(6.5 %)	0	(0 %)	
Extranodal extension					<0.001
No	74	(53.2 %)	142	(87.1 %)	
Yes	65	(46.8 %)	21	(12.9 %)	
Metastasis level-III-node					<0.001
No	89	(64.0 %)	151	(92.6 %)	
Yes	40	(28.8 %)	12	(7.4 %)	
Unknown	10	(7.2 %)	0	(0 %)	

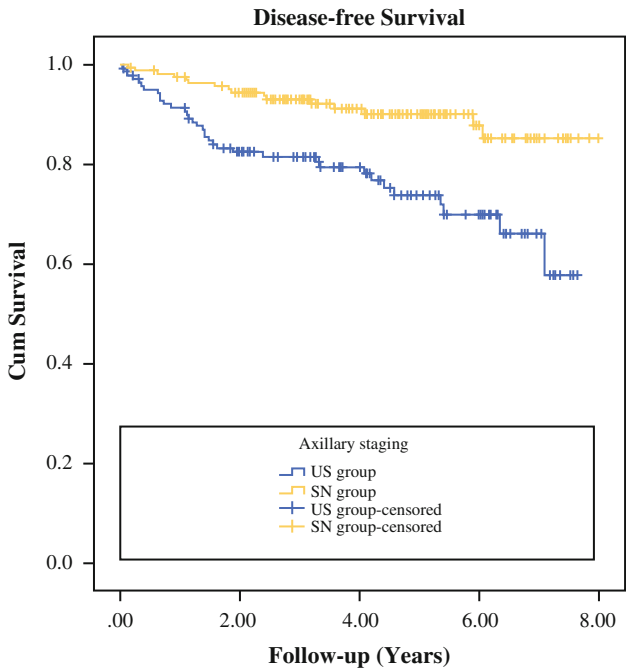

FIG. 2 Kaplan-Meier curve of disease-free survival of patients with a positive SLNB and patients with a positive UGLNB (p = 0.001). SN group = sentinel node-positive patients; US group = patients with a positive ultrasound-guided lymph node biopsy

(p < 0.0001). Subsequent Cox regression analysis resulted in a hazard ratio (HR) of 2.71 (95 % CI, 1.49–4.92) for the US group compared with the SN group (Fig. 2).

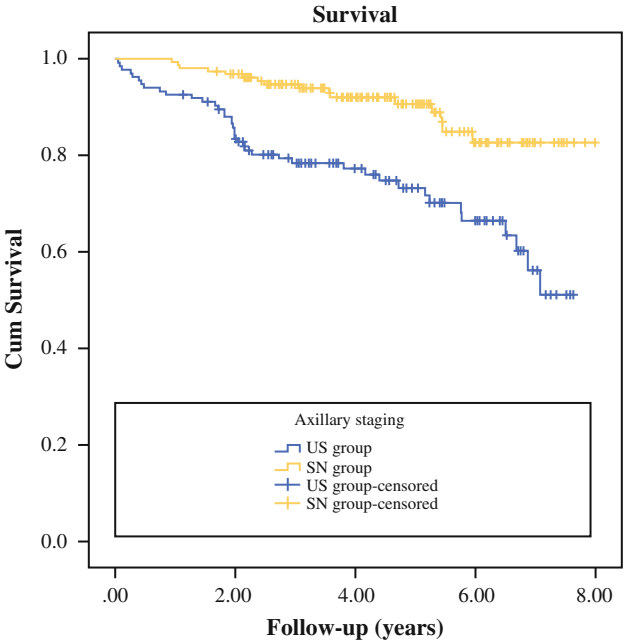

FIG. 3 Kaplan–Meier curve of overall survival of patients with a positive SLNB and patients with a positive UGLNB (p < 0.001). SN group = sentinel node-positive patients; US group = patients with a positive ultrasound-guided lymph node biopsy

Furthermore, the 5-year overall survival rate was 73.0 % (95 % CI, 72.3–73.8) in the US group versus 82.4 % (95 % CI, 81.7–83.1) in the SN group (p < 0.001). Cox regression, adjusted for age at diagnosis, resulted in a HR of 2.67 (95 % CI, 1.48–4.84) for the US group compared with the SN group (Fig. 3).

When excluding patients with palpable lymphadenopathy, both overall survival and disease-free survival remained significantly worse for patients of the US group compared with the SN group (HR = 2.84; 95 % CI = 1.13–7.17) with respect to the disease-free survival and, after adjusting for age at diagnosis, a HR of 3.36 (95 % CI, 1.45–7.77) for overall survival.

DISCUSSION

The present study compared patient, tumor, and lymph node characteristics and differences in survival between patients with a positive UGLNB and patients with a positive SLNB. The results show that US-positive patients more often had clinically palpable lymphadenopathy and larger tumors with worse prognostic factors, such as a higher tumor grade and lymphovascular invasion. Consequently, these differences may explain the higher proportion of radical mastectomies and the larger tumor burden in the axilla, resulting in a worse disease-free and overall survival in patients diagnosed by ultrasound. Similar differences were observed after exclusion of patients

with clinical palpable axillary nodes, indicating that patients selected by ultrasound represent a different breast cancer population.

Results from the ACOSOG Z0011 trial caused a paradigm shift in future management of invasive breast cancer. Due to the Z0011 trial, many breast cancer patients with a positive SLNB, treated with breast conservational therapy, may now be spared an ALND. The question of which technique is used to diagnose an axilla as node positive is therefore very relevant. Whether the conclusions of the Z0011 trial also could be applied to patients selected by ultrasound should be established by firstly examining whether these patient populations are comparable with regards to patient and tumor characteristics. Our findings show that patients whose axillary nodal status is proven to be positive by either the SLNB or UGLNB differ substantially from each other with respect to various characteristics, even when excluding patients with palpable lymphadenopathy. The literature has shown that increased tumor size, higher tumor grade, lymphovascular invasion, extranodal extension, size of metastases, ER/PR negativity, and number of positive lymph nodes are predictive factors for a worse prognosis.[2,8,9,17,18] In our study population, US-positive patients more often had tumors with the majority of these characteristics and a higher number of metastasized lymph nodes than SN positive patients, which can obviously explain the worse prognosis. These results are in accordance with the results of Wely et al., who concluded that patients diagnosed after an UGLNB more often had extensive nodal involvement.[19] However, Cools-Lartigue et al. also compared characteristics between such groups but did not find any significant differences, except for size of axillary metastases and Her2Neu status.[20] This, however, might be due to the small study population of only 76 patients.

Intuitively, it seems logical that patients with more axillary tumor burden are more easily discovered or identified by radiologists than those with less tumor load. However, with increasing improvement of radiological techniques, facilities, and experience the chance of finding axillary metastases will increase. Currently, various studies show that the overall sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the UGLNB is 50–70, 100, 100, 64–75, and 75 %, respectively, when conducted by an experienced radiologist.[19,21–23] However, these rates vary widely in published articles because of its high operator dependency. To improve the accuracy in preoperative diagnosis Swinson et al. recommended sampling multiple lymph nodes with an abnormal morphology.[13] Consequently, increasing sensitivity of axillary ultrasound will result in identifying more lymph node positive patients and thereby fewer differences with SN positive patients. This could lead to a larger group of patients being denied the chance of selection for the criteria described in the Z0011 trial, putting them at risk to the morbidity of an ALND, such as pain, loss of function, and edema.[9,10] This brings us to the present diagnosis-treatment paradox: the better the radiologist (or imaging procedure) can identify axillary metastases, the worse the surgical consequences for the patient.

Throughout the years, multiple prediction models have been developed to identify patients with a positive SN in whom the ALND can be omitted safely.[8,10,24–27] However, it is important to realize that due to the current differences in international guidelines with respect to the axillary workup, SN- and US-positive patients may represent a different patient population throughout the international literature. This may partially explain why existing prediction models are poorly implementable worldwide.[25,26,28]

Based on our findings, showing a substantial difference between US- and SN-positive breast cancer patients, the role and application of ultrasound in axillary staging needs to be redefined. In our opinion, axillary ultrasound should be employed to identify patients with extensive nodal involvement who may still benefit from nodal treatment, either by regional radiotherapy or surgery.[19,29,30] The radiologist therefore should focus on describing the number of suspected involved axillary lymph nodes.

Some considerations have to be taken into account. In our center, from 2006 until 2011 radiological examinations of the axilla were performed by general radiologists, without specific specialization in breast cancer imaging at that time. In centers with more specialized radiologists, however, the findings may be significantly different from ours. Moreover, we used retrospectively collected data. As a result, missing values occurred especially in the descriptive parameters of ultrasound findings and histopathological characteristics of the sentinel node biopsy. Furthermore, this study is a single-center study resulting in a relatively small population of only 302 cases over a period of 6 years.

Nevertheless, the present analysis reflects a common and general patient population with invasive breast cancer as can be seen in most peripheral nonacademic (teaching) hospitals.

CONCLUSIONS

The results of this study suggest that patients with positive axillary lymph nodes identified by ultrasound are substantially different with respect to tumor characteristics, extent of axillary nodal disease and (disease-free) survival compared with patients selected by a sentinel lymph node procedure, regardless of clinical palpability of the axillary lymph nodes. Considering these differences in characteristics, the conclusions of the ACOSOG Z0011 trial seem as yet only applicable to patients with a positive axilla found by SNLB. However, to establish conclusively whether the

Z0011 conclusions also could be applied to US-positive patients, further research comparing both axillary US- and SN-positive patients should be performed. Also, based on these results, we recommend that the role of ultrasound in axillary staging has to be redefined to identify patients with extensive node involvement.

CONFLICT OF INTEREST None to declare.

DISCLOSURE None to declare.

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