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● *Original Contribution*

PRE-OPERATIVE ULTRASONOGRAPHIC EVALUATION OF AXILLARY LYMPH NODES IN BREAST CANCER PATIENTS: FOR WHICH GROUP STILL OF ADDITIONAL VALUE AND IN WHICH GROUP CAUSE FOR SPECIAL ATTENTION?

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Abstract—A non-invasive and widely available method for pre-operative evaluation of the axilla is axillary ultrasonography (US). The purpose of this study was to evaluate the diagnostic accuracy of axillary US and fine-needle aspiration cytology in a large cohort of breast cancer patients. The sensitivity and specificity of US and fine-needle aspiration cytology in our cohort of 1124 patients were 42.2% and 97.1%, respectively. As the number of axillary nodes increased, sensitivity increased. The percentage of false-negative US results was 18.9%; patients in this subgroup were significantly younger, had larger tumors, more often had lymph vascular invasion and were more likely to have estrogen receptor-positive tumors. Ultrasonography in combination with fine-needle aspiration cytology is useful in the pre-operative workup of breast cancer patients, especially patients with three or more nodal metastases. Special attention should be paid to younger women with larger tumors in whom a larger percentage of false-negative results are obtained. (E-mail: y.moorman@zgt.nl) **© 2015 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Breast cancer, Pre-operative staging, Axillary ultrasonography, Fine-needle aspiration cytology, Sentinel lymph node biopsy, Axillary lymph node dissection, False-negative ultrasonography.**

INTRODUCTION

Over the years there has been growing interest in the development of clinical prediction tools to estimate the risk of patients with breast cancer having axillary nodal metastases, thereby making it possible to plan specific therapies. Sentinel lymph node biopsy (SLNB) has become the standard method of axillary lymph node staging in patients with invasive breast cancer. It has replaced axillary lymph node dissection (ALND), as it is associated with significantly lower morbidity (Purushotham et al. 2005). However, SLNB is still an invasive method and has a 4%–14% rate of complications such as lymphedema, seroma, paresthesia, chronic pain and immobility (Temple et al. 2002). When node metastases are found with SLNB, ALND is still warranted, which means that the patient has to undergo a second operation. Not only is this an inconvenience for the patient, but it also results in more operating time, space and costs (Boughey et al. 2010).

A non-invasive and widely available screening method is axillary ultrasonography (US). Pre-operative axillary US, with or without fine-needle aspiration cytology (FNAC) of lymph nodes suspicious for metastases, is now routinely performed in many breast cancer centers (Glynn et al. 2010). The utility of axillary US in detecting nodal metastases has been studied extensively. The results vary widely, especially in patients with early-stage breast cancer (Alvarez et al. 2006; Garcia Fernandez et al. 2011; Mainiero et al. 2010). The sensitivity and specificity of axillary US range between 40% and 92%, and between 56% and 100%, respectively. Specificity increases to 100% with the use of FNAC. However, as with all US procedures, the sensitivity and specificity of axillary US depend strongly on the experience of the ultrasonographer and the reference standard for malignancy used. The majority of previous studies on axillary US and FNAC

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have studied small patient groups (<500 patients) and have used different morphologic criteria for detecting nodal metastases: palpable versus non-palpable nodes, inclusion or exclusion of micrometastases and differences in the prevalence of axillary nodal burden (Alvarez et al. 2006; Bonnema et al. 1997; Cho et al. 2009; de Freitas et al. 1991; Jung et al. 2010; Motomura et al. 2001; Rajesh et al. 2002; Vaidya et al. 1996; Verbanck et al. 1997; Yang et al. 1996).

The aim of this study was to evaluate the utility and diagnostic accuracy of axillary US and US with FNAC in detecting axillary lymph node metastases in a large cohort of breast cancer patients.

METHODS

Patients

This retrospective cohort study was conducted in the Hospital Group Twente, a large teaching hospital located in Almelo and Hengelo, The Netherlands. Approval from the institutional review board was not required because this was a non-interventional retrospective study using known data. From January 2007 until July 2011, 1124 consecutive primary breast cancer patients were selected. These patients were both screen detected and/or symptomatic. All patients underwent pre-operative axillary US and subsequent surgery with SLNB and/or ALND according to current Dutch guidelines. Patients with palpable axillary disease, clinical and radiologic T4 status, ipsilateral recurrent breast malignancy and neo-adjuvant chemotherapy were excluded.

Pre-operative ultrasonography and fine-needle aspiration

All patients underwent routine mammography, ultrasonography of the breast and ipsilateral ultrasonography of the axilla by a trained radiologist or a radiology resident under the supervision of a trained radiologist. Two commercial ultrasound scanners were used; the Acuson X300/VF13-5 transducer (Siemens, Seongnam, South Korea), with a frequency bandwidth of 4.4–13.0 MHz and a maximum field of display of 61 mm, and the Aloka Prosound Alpha 7/UST-5412 transducer (Aloka, Tokyo, Japan), with a frequency bandwidth of 5–13 MHz and maximum field of display of 60 mm. These were located at different sites, so the ultrasound scanner used was the one available in the hospital where patients presented. A lymph node was classified as suspicious if its cortical thickness was >2.3 mm or if it had an irregular nodular cortex and/or a diminished or absent hilum (Deurloo et al. 2003). When suspicious nodes were found, US-guided FNAC was performed using a 21-gauge needle, and the aspirate was sent to the pathology department for cytologic analysis. If needed, a second attempt was made. FNAC analysis was carried out after Giemsa and Papanicolaou staining (Surepath).

SLNB and ALND protocol

The study protocol is summarized in Figure 1. Patients with non-suspicious nodes after axillary US and those with no malignant cells after FNAC (or from whom insufficient material was obtained for diagnosis after several attempts) were scheduled for SLNB. Sentinel lymph nodes (SLNs) were harvested after scintigraphy and patent blue dye injection during or immediately before surgery by one of our experienced breast surgeons or by a surgical trainee under the strict supervision of an experienced breast surgeon. A sentinel node was identified as any blue-staining node, hot node or node with at least 10% of the highest hot node count. Pathologic examination classified SLNs as macrometastases (>2 mm), micrometastases (0.2–2 mm) or isolated tumor cells (<0.2 mm). If US-guided FNAC proved positive for malignant cells, ALND was performed. Complete ALND was routinely performed when a metastasis was present in the SLN. In this study, we focused on macrometastases, because micrometastases do not normally alter the morphology of the lymph node and are thereby difficult to detect (Garcia-Ortega et al. 2011).

Patient and tumor characteristics were retrieved from the original patient files. The final pathology results, based on SLNB and/or ALND, were correlated with axillary US alone or US in combination with FNAC.

Statistical analysis

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for axillary US alone and axillary US in combination with FNAC, with the final pathologic findings with SLNB and/or ALND as gold standard. The utility of US and US with FNAC was assessed by determining the positive and negative likelihood ratios. The correlation between clinic and pathologic variables and false negativity of axillary ultrasonography was analyzed using the χ^2 test. A p value < 0.05 was considered to indicate statistical significance.

RESULTS

Patient and tumor characteristics

During the observational period from January 2007 until July 2011, 1178 patients were treated for primary invasive breast cancer in the Hospital Group Twente, The Netherlands. Of these patients, 20 had palpable axillary lymph nodes and 34 patients, did not undergo the routine workup for other reasons, leaving 1124 patients for further analysis. All patients had solitary tumors. The median age of the patients was 61 y

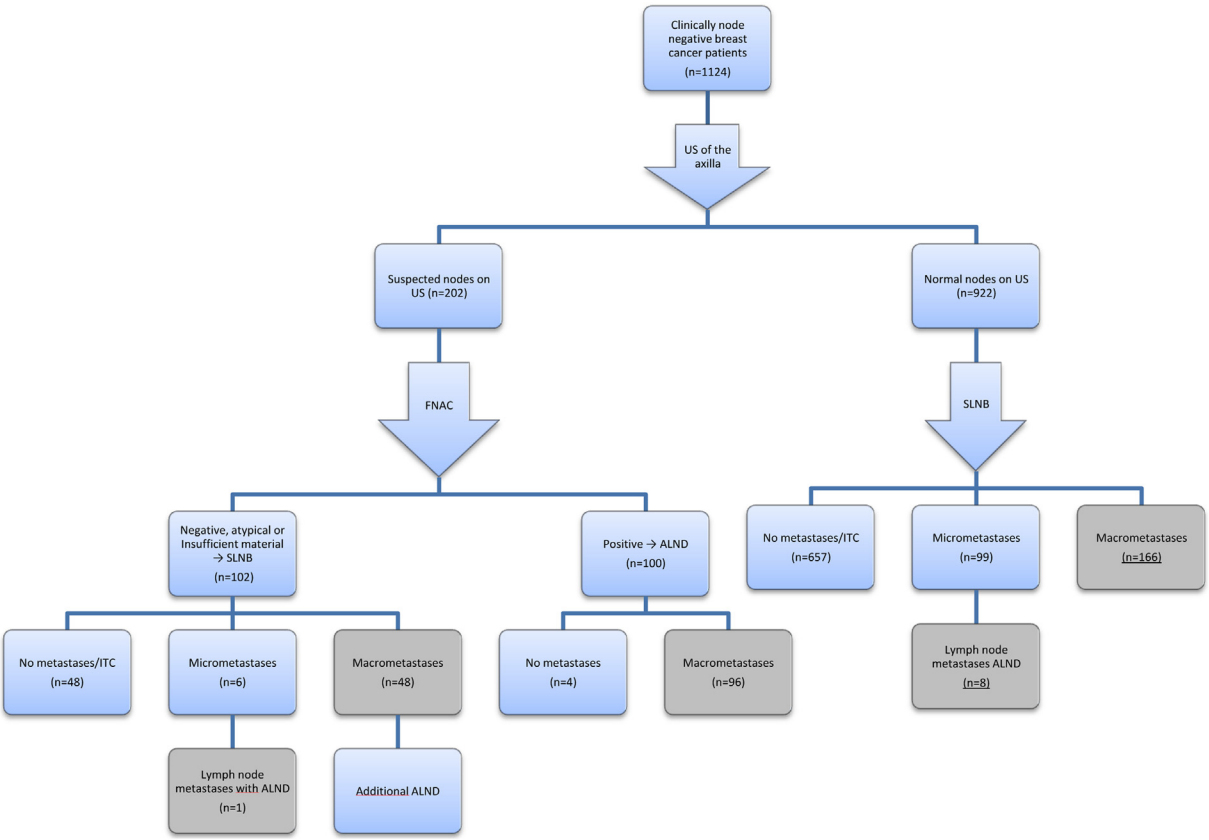

Fig. 1. Study algorithm. Grey coloured boxes = total of patients with lymph node metastases; Underlined boxes = total of patients with false-negative ultrasonography.

(range: 24–93 y). The mean primary breast cancer tumor size was 20.46 mm (range: 1–130 mm). When the tumors were subdivided by tumor stage, 59.5% were T1, 35.3% were T2, 4.9% were T3 and 0.2% were pathologic T4 tumors. There were 910 invasive ductal carcinomas, 138 invasive lobular carcinomas, 15 mixed ductal and lobular carcinoma and 61 other carcinomas (total n = 1124). The median number of nodes removed with sentinel node biopsy was 2 (range: 1–13).

US in relation to the number of axillary nodal metastases

The overall percentage of axillary (macro) metastases was 28.4%. Of the 1124 patients, 922 (82.0%) had no suspicious axillary lymph nodes on US, and 202 (18%) did have suspicious nodes. The sensitivity of US in determining nodal involvement was 45.5% in the case of one nodal metastasis, with a specificity of 92.9%. The positive predictive value (PPV) and negative predictive value (NPV) were 71.8% and 82.0%, respectively. The positive likelihood ratio (+LR) was 6.41 and the negative likelihood ratio (–LR) was 0.59. In the case of two nodal metastases, US sensitivity was 56.9%, specificity 92.9%, PPV 64.4%, NPV 90.6%, +LR 8.01 and–LR 0.46. In the case of three or more nodal metastases, sensitivity was 60.8%, specificity 92.9%, PPV 58.1%, NPV 93.6%, +LR 8.56 and–LR 0.42 (Table 1). Total number of patients decreased with increasing number of nodal metastases as we compared patients with one or more, two or more and three or more macrometastases with no metastases.

US in combination with FNAC

FNAC was performed on all nodes that were considered suspicious with axillary US. The positive US/positive FNAC group consisted of those patients who were found to have suspicious nodes on axillary US and were proven to have a malignancy after FNAC. Also included in this group were patients in whom atypical cells were found with FNAC and patients whose cytologic specimens were inadequate for evaluation. The sensitivity of US with FNAC in determining nodal involvement was 42.2%, specificity 97.1%, PPV 85.2%, NPV 81.2%, +LR 15.6 and–LR 0.59. The respective numbers for two and three nodal metastases are listed in Table 1. The total number of patients within this group also decreased with increasing number of nodal metastases, as we compared patients with a positive US and positive

Table 1. Accuracy and utility of US and US in combination with FNAC subdivided by number of axillary nodal metastases

	N	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	+LR	–LR
Positive US*							
Overall	1124						
1 metastasis	319	45.5	92.9	71.8	82.0	6.41	0.59
(minus micro†)	311	46.6	92.5	73.2	79.8	6.21	0.58
2 metastases	181	56.9	92.9	64.4	90.6	8.01	0.46
3 metastases	130	60.8	92.9	58.1	93.6	8.56	0.42
Positive US with positive FNAC‡							
Overall	1071						
1 metastasis	301	42.2	97.1	85.2	81.2	15.6	0.59
(minus micro†)	293	43.3	97.3	87.6	79.8	16.0	0.58
2 metastases	175	55.4	97.1	81.5	90.6	19.1	0.46
3 metastases	127	59.8	97.1	77.6	93.6	20.6	0.41

FNAC = fine-needle aspiration cytology; +LR = positive likelihood ratio; –LR = negative likelihood ratio; Metastases = number of micro- or macrometastases found with sentinel lymph node biopsy or axillary lymph node dissection; NPV = negative predictive value; PPV = positive predictive value; US = ultrasonography.

* Positive US = axillary US suspicious for malignancy versus axillary US with no suspicious nodes (negative US).

† If micrometastases would have been excluded from the population. Only 8 patients had additional metastases after axillary lymph node dissection of which only 1 had >3 metastases.

‡ Positive US + positive FNAC/atypical cells versus negative US.

FNAC with those with negative US. In analysis of sensitivity for two nodal metastases, patients with only one nodal metastasis are not automatically placed in the negative group, but were removed from further analysis.

False-negative axillary ultrasonography

Of the 922 patients with negative US, 18.9% had a false-negative ultrasound. These patients were found to have positive nodes after SLNB and/or ALND. Patient and tumor characteristics were compared between the true-negative and false-negative groups, and results are summarized in Table 2. Patients with false-negative axillary US were younger, had larger tumors, more often had lobular carcinomas, were found to have lymph vascular invasion (LVI) and were more likely to have estrogen receptor (ER)- or progesterone receptor (PR)-positive tumors. Univariate and multivariate analyses are outlined in Table 3. Age, LVI, ER status and pathologic tumor size remained significant after multivariate logistic regression analysis. For a patient <50 y of age who has a tumor ≥20 mm, the chance of a false-negative US is 45.9%, almost one in two patients.

Influence of micrometastases in the population

Sentinel lymph node biopsy revealed micrometastases in 103 patients. Of these patients, only 8 were found to have macrometastases after ALND and only 1 had three or more additional positive axillary nodes. Of the 4 patients found to have suspicious nodes with axillary ultrasonography, none had any additional axillary disease after ALND. If this population had been excluded from the study group, the values for sensitivity, specificity, and so on would have differed slightly (see Table 1).

Table 2. Differences in patient and tumor characteristics between false-negative and true-negative axillary ultrasonographic scans

Variable	True negative N = 748	False negative N = 174	*p* Value < 0.15
Age (y)			
<50	97 (13.0%)	56 (32.2%)	<0.001
≥50	651 (87.0%)	118 (67.8%)	
Clinical tumor size			
0–19 mm	551 (75.1%)	100 (59.2%)	<0.001
≥20 mm	183 (24.9%)	69 (40.8%)	
Histology			
IDC	606 (81.0%)	139 (79.9%)	0.011
ILC	84 (11.2%)	30 (17.2%)	
Other	58 (7.8%)	5 (2.9%)	
Histologic grade			
1	252 (34.0%)	42 (24.1%)	0.025
2	326 (44.0%)	94 (54.0%)	
3	163 (22.0%)	38 (21.8%)	
Multifocality			
No	665 (88.9%)	142 (81.6%)	0.008
Yes	83 (11.1%)	32 (18.4%)	
Lymph vascular invasion			
No	679 (90.8%)	127 (73.0%)	<0.001
Yes	69 (9.2%)	47 (27.0%)	
Estrogen receptor			
Negative	120 (16.2%)	12 (6.9%)	0.001
Positive	622 (83.8%)	162 (93.1%)	
Progesterone receptor			
Negative	222 (29.9%)	34 (19.5%)	0.006
Positive	520 (70.1%)	140 (80.5%)	
Her2/Neu			
Negative	666 (89.8%)	161 (92.5%)	0.320
Positive	76 (10.2%)	13 (7.5%)	
Pathologic T stage			
1a–c	524 (70.1%)	78 (44.8%)	<0.001
2	213 (28.5%)	78 (44.8%)	
3	11 (1.5%)	17 (9.8%)	
4	0 (0.0%)	1 (0.6%)	

Her2/Neu = human epidermal growth factor *receptor* 2; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma.

Table 3. Univariable and multivariable associations between patient/tumor characteristics and false-negative ultrasonography

	Univariable *p* value	Hazard ratio (95% CI)	Multivariable *p* value	Hazard ratio (95% CI)
Age (y)				
<50				
≥50	<0.001	3.185 (2.172–4.671)	<0.001	3.077 (2.006–4.719)
Clinical T stage rounded				
1a–c				
2	<0.001	2.078 (1.465–2.946)	0.436	1.190 (0.768–1.842)
Histology				
IDC				
ILC	0.057	1.557 (0.987–2.456)	0.151	1.459 (0.871–2.444)
Remainder	0.040	0.376 (0.148–0.954)	0.164	0.505 (0.193–1.321)
Tumor grade				
1				
2	0.007	1.730 (1.161–2.579)		
3	0.171	1.399 (0.865–2.263)	—	
Multifocality				
No				
Yes	0.009	1.806 (1.156–2.821)	0.340	1.281 (0.770–2.131)
Lymph vascular invasion				
No				
Yes	<0.001	3.642 (2.402–5.522)	<0.001	3.028 (1.872–4.895)
Estrogen receptor				
Yes				
No	0.002	2.605 (1.404–4.832)	<0.001	4.592 (2.304–9.149)
Progesterone receptor				
Yes				
No	0.007	1.758 (1.171–2.639)	—	
Pathologic T-stage				
1a–c				
≥2	<0.001	2.879 (2.055–4.034)	<0.001	2.224 (1.454–3.402)

Her2/Neu = human epidermal growth factor *receptor* 2; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma.

Because ALND is still advised after detection of micrometastases according to Dutch guidelines, we did not exclude this group from our analysis.

DISCUSSION

In the present study, we assessed the accuracy and clinical utility of routine pre-operative axillary US in combination with FNAC in patients with breast cancer in The Netherlands. The prevalence of nodal metastases (macrometastases) in our study was 28.4%. Our study suggests that specificity and PPV in detecting axillary metastases were higher for patients who underwent axillary US in combination with FNAC, especially those with gross nodal disease, than for patients who underwent US alone. Tahir et al. (2008) reported an increase in sensitivity from 47.1% to 80% when two or more nodal metastases were found. Sensitivity, on the other hand, was lower for US + FNAC than for US alone, as also reported in the literature (Leenders et al. 2012; Park et al. 2011).

Ultrasonography of the axilla is a useful diagnostic technique for the evaluation of axillary lymph nodes because it is non-invasive, widely available and easily incorporated into the standard workup for breast cancer patients. Its sensitivity and specificity vary greatly in the literature, ranging from 40% to 92% and from 56% to 100% respectively (Alvarez et al. 2006; Bonnema et al. 1997; de Freitas et al. 1991; Jung et al. 2010; Motomura et al. 2001; Rajesh et al. 2002; Vaidya et al. 1996; Verbanck et al. 1997; Yang et al. 1996). Specificity increases when US is combined with FNAC, but sensitivity continues to vary greatly. There are a number of reasons for this discrepancy. First, the prevalence of axillary metastases in the study populations differs greatly, ranging between 25% and 58% (Leenders et al. 2012). In our study, the prevalence of nodal metastases was 28.4%, which is relatively low compared with values in the literature. Because PPV and NPV are directly proportional to the prevalence of the disease, these would increase with higher prevalence. To overcome this problem we also calculated the +LR and–LR, as these are not influenced by prevalence.

Second, patient selection differs. Our patients had relatively early breast cancers, with nearly 60% T1 tumors. A third reason for the observed differences is the exclusion criteria. Some studies include both palpable and non-palpable nodes, which are of great significance in analyzing accuracy. If we would have included palpable nodes and cT4 tumors, our sensitivity would have increased. Finally, the criteria used for node morphology and needle biopsy differ. In our study we performed FNAC on suspicious nodes, whereas some

studies performed FNAC on all lymph nodes ultrasonographically visualized independently of their appearance or size (Altomare et al. 2007; Alvarez et al. 2006; Bonnema et al. 1997; de Kanter et al. 1999, Fant et al. 2003; Holwitt et al. 2008; Kuenen-Boumeester et al. 2003; Mansel et al. 2006; Sapino et al. 2003). Some studies used nodal size as a criterion for malignancy, and others used morphologic criteria (Cools-Lartigue et al. 2013; Houssami et al. 2011). In our study, the cutoff point for malignant node size was 2.3 mm; inter-observer variation is to be expected with a cut-off behind the decimal point.

Results from the American College of Surgeons Oncology Group (ACOSOG) Z0011 (Giuliano et al. 2011) randomized controlled trial, however, revealed equivalent survival and regional control in patients with T1–T2 tumors, a maximum of two macrometastases with SLNB and additional radiation therapy with or without additional ALND. These observations would suggest a diminishing role for pre-operative US and FNAC in this population. In this study, pre-operative US and FNAC were of special value in patients with gross nodal disease, the subgroup that was excluded in the ACOSOG trial. Within this subgroup, ALND is still of additional value.

Because sensitivity is often found to be low, we also investigated the clinical–pathologic variables associated with patients with false-negative US. The total rate of false-negative results in our series was 18.9%. Patients with false-negative axillary US were significantly younger, had larger tumors, more often had lymph vascular invasion and were more likely to have ER-positive tumors. Lobular histology and PR positivity were more often observed within this subgroup, although these factors did not remain significant after multivariate analysis. In the literature, the percentages of false-negative US and FNAC range between 28.1% and 31% (Johnson et al. 2011; Leenders et al. 2012, 2013). These patients were younger, had larger tumors, had tumors that were lobular (although not always significant) and had lymph vascular invasion (Choi et al. 2012; Johnson et al. 2011; Leenders et al. 2013). The reasons are not always clear. Johnson et al. (2011) state that a false-negative US is more likely in larger tumors and tumors with lymph vascular invasion because of the higher pre-test probability of metastatic disease. The correlation of ER positive tumors and false-negativity is unknown. The prevalence of false negativity and PR positivity might be correlated with a higher risk of node metastases in PR-positive tumors (Ravdin et al. 1994; Viale et al. 2005). Although not always significant, there was a tendency toward lobular carcinomas in the false-negative group. Lobular carcinomas are known to be harder to diagnose with US; perhaps the same also supplies for the detection of nodal metastases (Lopez and Bassett 2009).

CONCLUSIONS

Ultrasonography in combination with FNAC is useful in the pre-operative workup of breast cancer patients. Patients with early-stage breast cancer are unlikely to have heavy axillary disease burden, and in this subgroup the value of ALND has recently been up for discussion. Within the group of patients with three or more nodal metastases, however, the accuracy of US and FNAC is much higher and will be of additional value. Special attention should be paid to younger woman with larger tumors, in whom a larger percentage of false-negative results are obtained. US and FNAC are of lower sensitivity, and direct SLNB might be preferred.

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