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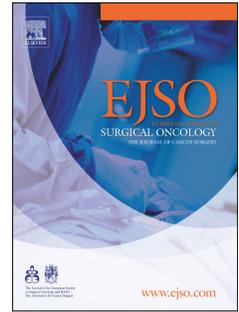
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Ultrasound and fine needle aspiration cytology of the axilla in the pre-operative identification of axillary nodal involvement in breast cancer

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Abstract

Background: Preoperative diagnosis of axillary nodal involvement in breast cancer allows one-stage axillary surgery. We evaluated the efficacy of axillary ultrasound (US) with US guided fine needle aspiration cytology (FNAC) in the diagnosis of axillary nodal involvement.

Materials and Methods: Over a 13-month period, we performed US of 369 axillae in patients with screen-detected (n=278) and symptomatic (n=91) invasive carcinoma of the breast, at the same time as US of the primary tumour. If abnormal lymph nodes were demonstrated, a single US guided FNAC of the most abnormal node was performed. US and FNAC results were compared with the final histology of the surgically excised lymph nodes.

Results: Among the 369 axillae studied, 102 had nodal macrometastases and 38 (37%) were identified by US guided FNAC. The rate was 33% in screen-detected and 44% in symptomatic patients. Sensitivity increased with increasing numbers of positive axillary nodes, and the more abnormal the appearances of the nodes on US.

Conclusion: US with FNAC of the most abnormal node allows preoperative detection of a third of node positive axillae in screen-detected and over 40% of those with symptomatic breast cancer, allowing one-stage axillary surgery avoiding the sentinel node biopsy step in these patients.

Introduction

Preoperative identification of axillary node positivity in breast cancer patients would allow one-stage axillary clearance, avoiding the sentinel node biopsy (SLNB) step. It may also have an impact on the decisions to offer neoadjuvant therapy and immediate reconstruction of the breast. As clinical examination is unreliable in determining node positivity, preoperative diagnosis presently depends on imaging of the axilla. Various imaging modalities such as mammograms, scintimammography, ultrasound (US), computed tomography, magnetic resonance imaging, and positron emission tomography have been studied in the detection of axillary nodal involvement. While the sensitivity and specificity of these imaging modalities do not match that of the SLNB, when combined with fine needle aspiration cytology (FNAC) or core biopsy (CB) of the abnormal lymph node, some of them do allow the preoperative detection of a proportion of node positive patients who could then proceed directly to an axillary clearance. US is well suited for this role as most patients with breast cancer nowadays undergo US and US-guided CB of the primary tumour, thus the ipsilateral axilla could be scanned at the same time. We evaluated the efficacy of axillary US combined with US guided FNAC in the diagnosis of axillary nodal involvement in patients presenting with screen-detected and symptomatic invasive breast cancer.

Patients and methods

We adopted routine axillary US of patients presenting with suspected invasive breast carcinoma in our practice in year 2006. From June 2006 to August 2007, we prospectively audited patients presenting at our centre through the

National Health Service Breast Screening Programme or through the rapid diagnosis symptomatic breast clinics with suspected invasive cancer who underwent US of the ipsilateral axilla. The primary tumour in the breast underwent US first and, if an invasive carcinoma was suspected, axillary US was performed at the same time. Particular attention was paid to the lower axilla, posterior to where the pectoralis muscle crosses the cranial edge of the breast, as this is a common location for the sentinel node¹. The nodes, when visualised, were assessed for the shape and the morphology of the cortex. Nodes were classified as abnormal if their longitudinal to transverse ratio was < 2 and / or the cortex was concentrically or eccentrically thickened to $> 2\text{mm}^2$. Core biopsies (CB) were taken from the primary tumour for confirmation of diagnosis and where abnormal nodes were seen, a single US guided FNAC of the node was carried out using a 10 ml syringe attached to either a 21 or 23 gauge needle. If more than one node was found to be abnormal, the sample was taken from the node considered to be the most abnormal. US and FNAC's were performed by seven consultant breast radiologists and 2 breast clinicians using a 14MHz transducer with a Toshiba Aplio (Toshiba Medical Systems Ltd, Crawley, UK) machine, except in the case of a small number of symptomatic patients (n=13) who were evaluated using a 13 MHz transducer with an Esaote AU5 (Esaote UK, High Wycombe, UK) machine.

Patients were excluded from the analysis if they were treated medically, if they had no / inadequate axillary nodal surgery, or had negative axillary US + / - FNAC and had neoadjuvant chemotherapy prior to any form of axillary surgery. However, patients who had unequivocally positive axillary FNAC but

negative axillae on clearance following neoadjuvant chemotherapy were included.

Patient details and US, CB and FNAC findings were recorded prospectively. The axillae of patients who underwent adequate staging of the axilla by surgical excision of the axillary lymph nodes by sentinel lymph node biopsy (SLNB), axillary sampling, or clearance were included in the analysis. As our screening service covers a larger population than our symptomatic service, some women with screen-detected breast cancers underwent surgery at their local breast surgical unit following diagnosis. Other screen-detected cancers and all symptomatic cancers in the study were treated at our centre. Details of treatment and final histology were collected on all patients and the initial axillary US and FNAC results were compared with the final histology of the lymph nodes.

Results

Results are presented in Table 1. During the study period 461 new, early invasive cancers (326 screen-detected and 135 symptomatic) in 455 women were diagnosed at our centre. US of the ipsilateral axilla was performed in 408 (293 screen-detected and 115 symptomatic) instances. Fifty three axillae were not scanned; omission of axillary US in screen-detected invasive cancers was mainly due to initial imaging not being suggestive of invasive cancer. In cancers presenting symptomatically, omissions were due mainly to clinically obvious lymph node involvement or due to large tumours in patients unfit for surgery where CB of the primary tumour was performed clinically without US guidance. Over the study period 69 (56 screening, 13 symptomatic) patients

without invasive cancer had an axillary US because initial imaging was suspicious of an invasive cancer. The axillae of these patients are not considered any further.

Of the 408 axillae scanned, 38 (14 screen-detected and 24 symptomatic) were excluded from analysis because the patients were treated medically or had negative axillary US + / - FNAC and had neoadjuvant chemotherapy prior to axillary surgery. Two patients who had unequivocally positive axillary FNAC but negative axillae on clearance following neoadjuvant chemotherapy which resulted in a pathological complete response of the primary tumour were included. One axilla (screen-detected) was excluded because of an inadequate axillary procedure. Final surgical histology is available for 369 axillae (287 screen-detected and 91 symptomatic) and this constitute the final study group.

Among the axillae of patients presenting symptomatically (n=91), there were palpable nodes in 19. Reliable palpability data is not available for the axillae of screen-detected patients as axillary US and FNAC were carried out prior to clinical assessment by a surgeon, but our experience with the axillae of screen detected patients treated at our centre during the study period suggested it was no more than 3%.

Among the 369 axillae in the final study group, 360 were initially treated by surgery (276 screen-detected and 84 symptomatic). The remaining 9 were treated with neoadjuvant therapy; 7 (2 screen-detected and 5 symptomatic) following a positive axillary FNAC, and 2 (both symptomatic) following SLNB carried out after a negative axillary assessment. Overall, 116 axillae out of 369 (31.4%) had positive axillary nodes (102 with macrometastases and 14

with micrometastases) and 38 of these (33%) were identified preoperatively. Among the 14 axillae with micrometastases, axillary US revealed an abnormal node in one, but the FNAC was benign, thus none of the axillae with micrometastases were diagnosed preoperatively. The number of fine needle aspirates that were considered inadequate for cytological assessment and those thought to be indeterminate was low in our study, at 11% and 1.8% respectively.

Among 102 axillae (27.6% of the study population) with macrometastatic (≥ 2 mm) disease, 38 (37%) were identified preoperatively. Identification rates for nodal macrometastases were 33% (20/61) for screen-detected (n=278) and 44% (18/41) for symptomatic (n=91) cancers. The overall sensitivity of axillary US and FNAC in the diagnosis of macrometastatic disease was 37% and specificity 99.6%. The reason that the specificity did not reach 100% was due to one false positive FNAC. This patient had a screen-detected invasive lobular carcinoma and following an apparently positive FNAC underwent an axillary clearance where 16 nodes were removed and found to be negative for metastatic disease. A subsequent cytological review showed that crushed lymphocytes were mistaken for malignant cells.

Sensitivity of axillary US + / - FNAC in the detection of a positive axilla increased with increasing number of positive nodes in the axilla on final histology. Amongst axillae with more than 3 positive nodes, 50% (19/38) were identified as node positive preoperatively, whereas in axillae with only one node positive, the corresponding figure was 15% (5/33). The likelihood of positive FNAC increased the more abnormal the appearance of the axillary nodes. All 13 axillae with classically malignant nodes on US, and 17 of 24

(71%) with nodes with obviously abnormal cortices even when the hila were preserved turned out to be positive, whereas in axillae showing nodes with minor abnormalities, only 19/76 (25%) were positive.

Discussion

Value of pre-operative recognition of node positivity

Breast cancer patients with clinically negative axillae are staged with sentinel lymph node (SLN) biopsy and those with a positive SLN are recalled for axillary clearance. Such a recall causes distress to patients and their family, consume resources, and axillary clearance following previous SLNB is technically more difficult. Two ways that these problems can be minimised are by the identification of a positive axilla pre-operatively or a positive SLN intra-operatively. Intra-operative techniques include touch imprint cytology, frozen section, and more recently, RNA-based techniques. Intra-operative assessment has some drawbacks. Patients undergo surgery without knowing beforehand the surgical procedure that will be performed and planning of operating lists can be difficult. Intra-operative methods are also expensive, due to the cost of the test, theatre time wasted, or both. Pre-operative diagnosis of node positivity would allow the surgeon to inform the patient of her axillary status prior to surgery, and one-stage axillary clearance. This would reduce the number of patients requiring SLNB and intra-operative assessment.

Diagnostic rate of positive axillae in this study

This is one of the largest studies published to date on the use of axillary US and FNAC, and our overall preoperative identification rate for axillary node

macrometastases was 37%. A number of prospective studies looking at the role of axillary US for this purpose have been published (Table 2). With a few exceptions²⁻⁴ these have used FNAC rather than core biopsy. The pre-operative identification rate ranges from 21-90%²⁻¹⁴ but the studies are not directly comparable as they differ in the patient population studied, protocols for node sampling, number of samples taken, or the underlying node positivity rate in the population studied.

Our study is unique in that the majority of the cancers studied were screen-detected. Axillary node positivity is lower in these patients, around 24%¹⁵ compared with approximately 40-50% in those presenting symptomatically¹⁶. In this study the node positivity rate for macrometastatic disease was 22% (61/278) in screen-detected and 46% (41/91) in symptomatic cancers, giving an overall node positivity rate for macrometastatic disease of less than 28%. Sensitivity and specificity of a diagnostic test are affected by the prevalence of the disease in the study population. Despite a relatively low prevalence rate of node positivity in this study, US +/- FNAC diagnosed over a third of axillae with macrometastases pre-operatively. The sensitivity of the US increased with increasing tumour burden in the axilla, as measured by the number of positive nodes. This has also been observed in previous studies⁵.

Imaging assessment in a single sitting

We performed the US at the same time as the US of the primary tumour, before CB confirmation of invasiveness of the primary tumour was available. This was done to avoid having to recall patients on a separate occasion for axillary assessment. This approach resulted in some patients with invasive cancers missing out on axillary US and some patients without invasive cancer

having an axillary US. Despite this, in a large busy NHS breast-screening centre where a large number of breast-screening recall assessments are carried out and symptomatic patients seen in rapid diagnosis clinics, we found this approach practical, as it did not consume much extra time or resources. An additional axillary US only added a few more minutes to the imaging assessment of the patient, and the single FNAC, when performed, was again quick and relatively inexpensive.

Further improvement of diagnostic rate

It would have been feasible to recall those patients with invasive cancer who did not have axillary US at initial assessment at a later date. It also would have been feasible to take multiple samples. We sampled only the most abnormal node and performed only one FNAC per axilla for practical reasons. Sampling multiple abnormal nodes^{9, 13}, sampling multiple nodes including nodes with benign appearances thus lowering the threshold for FNAC⁵, taking multiple samples from one (or more) node may all improve the pre-operative diagnosis rate. However, patient acceptability (of multiple needle tests) and cost-benefit ratio (as more sampling takes more radiologist and cytologist time) should be considered.

Core biopsy of the axillary node has been attempted to improve the pre-operative diagnostic rate. In a small study of 39 patients with over 75% node positivity rate, CB produced a high preoperative diagnosis rate³, but in another study with a mix of patients more typical of that seen in the UK and elsewhere, there was no convincing evidence that CB was better than FNAC in preoperative diagnosis². A second CB (in addition to that of the primary tumour) in the same sitting may be unacceptable to the patient⁴, technically

difficult or impossible and have a higher risk of complications because of the proximity of axillary vessels²⁻⁴. In addition, it needs to be kept in mind that once multiple FNAC's or CB of the node(s) have proved negative, these patients would be subjected to a SLNB. The effect of such aggressive attempts at preoperative diagnosis on the subsequent SLN identification rate and false negative rate is not known. It is feasible that damage to afferent lymphatic vessels could occur that might interfere with subsequent SLNB⁷. Furthermore, axillary US could never result in 100% pre-operative diagnosis as we found that a third (33%) of macrometastases occur in patients in whom no axillary lymph nodes were identified on US. US also does not detect nodes with micrometastases, as shown by this study (14 cases) as well as other cases described in the literature^{4, 6, 7, 11, 14} where only one out of 92 axillae with micrometastases was identified pre-operatively. This must be due to micrometastases not altering the morphology of the node sufficiently for it to be detected by US.

False-positive FNAC

There was one false positive FNAC in our study in a patient with invasive lobular carcinoma. Due to the 'indian file' pattern of infiltration, lobular carcinoma infiltrating lymph nodes can be difficult to differentiate from lymphocytes, even for an experienced pathologist. Others^{8, 11, 12} have also reported false positive axillary lymph node FNAC but only in two cases the reasons have been discussed⁸. One was a multifocal breast tumour with a dense lymphocytic infiltrate, and the false positive FNAC was thought to have come from the most lateral breast focus, and another case resulted from a cytological misreading where cells interpreted as metastatic carcinoma cells

were apparently mesothelial cells presumably aspirated from the pleural cavity. False positives may be reduced by close co-operation and communication between the cytologist and the breast team doing the assessment, and double reading of axillary cytology where possible.

Conclusions

In conclusion, we found US guided FNAC of the most abnormal looking node at the same time as US assessment and CB of the primary tumour is a practical and cost-effective approach that allows pre-operative identification of a third of node positive axillae in screen-detected and over 40% of those with symptomatic breast cancers. The diagnostic yield increases with increasing number of positive nodes in the axilla.

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Conflict of interest

The authors state that they have no conflict of interest.

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Table 1

Pre-operative ultrasound (US) and fine needle aspiration cytology (FNAC) results in relation to axillary lymph node histology

Axillary node histology	US No nodes visualised	US Normal nodes	US – Abnormal nodes					Total
			FNAC Not done	FNAC Inadequate	FNAC Benign	FNAC Indeterminate	FNAC Malignant	
Macrometastases (≥ 2 mm)	34	18	-	3	8	1	38	102
<i>Screen-detected cancers</i>	26	10	-	-	4	1	20	61
<i>Symptomatic cancers^a</i>	8	8	-	3 ^b	4	-	18	41
Micrometastases (0.2 – 2 mm)	8	5	-	-	1	-	-	14
<i>Screen-detected cancers</i>	4	4	-	-	-	-	-	8
<i>Symptomatic cancers</i>	4	1	-	-	1	-	-	6

No metastases	125	65	3	9	49	1	1	253
<i>Screen-detected cancers</i>	103	52 ^c	3 ^d	8	41	1	1	209
<i>Symptomatic cancers</i>	22	13	-	1	8	-	-	44
Total	167	88	3	12	58	2	39	369
<i>Screen-detected cancers</i>	133	66	3	8	45	2	21	278
<i>Symptomatic cancers</i>	34	22	-	4	13	-	18	91

^a includes 2 axillae with unequivocally positive FNAC but negative axilla after neoadjuvant therapy where the primary tumours underwent complete pathological response

^b includes one axilla where FNAC was reported as inadequate because the preparation was thick. Final nodal histology showed chronic lymphatic leukaemia as well as breast cancer

^c includes one axilla negative on H&E staining but showed isolated tumour cells on immunostaining

^d FNAC not done in 2 cases due to needle phobia / patient anxiety, in one case a node identified and documented as abnormal could not be found again for FNAC

Table 2

Prospective studies of ultrasound guided sampling of axillary lymph nodes in invasive^a breast cancer

Authors	Year	FNAC or Core biopsy (CB)	Number of axillae included	Number (%) with palpable axillary nodes ^b	Number (%) of axilla positive ^c	Number (%) diagnosed pre-operatively	False positive FNAC / CB	Sampling protocol
Bonnema <i>et al.</i> ⁵	1997	FNAC	150	0	62 (41%)	39 (63%)	0	1-4 nodes regardless of echo pattern
De Kanter <i>et al.</i> ⁶	1999	FNAC	185	0	87 (47%)	31 (36%)	0	Largest or most suspicious node(s) up to a maximum of 2
Damera <i>et al.</i> ²	2003	CB (mainly)	166	10 (6%)	64 (39%)	27 (42%)	0	Single most suspicious node, 2 cores where possible. FNAC if core technically difficult

Duerloo <i>et al.</i> ⁷	2003	FNAC	268	0	121 (45%)	37 ^d (31%)	0	Single most suspicious node
Keunen-Bourneester <i>et al.</i> ⁸	2003	FNAC	183	0	85 (46%)	37 (44%)	3	Single node regardless of echo pattern, either most malignant-looking one or one closest to breast
Sapino <i>et al.</i> ⁹	2003	FNAC	267	Not stated	88 (33%)	49 (56%)	0	Suspicious nodes, one sampled initially. If more than 1 suspicious node, second sampled if initial node negative
Brancato <i>et al.</i> ¹⁰	2004	FNAC	159	67 (42%)	70 (44%)	38 (54%)	0	Single node regardless of echo pattern. Most suspicious node sampled

Podkrajsek <i>et al.</i> ¹¹	2005	FNAC	165	0	65 (39%)	32 (49%)	1	Suspicious nodes sampled. Not clear if single or multiple
Topal <i>et al.</i> ³	2005	Core	39	Not stated	33 (85%)	30 (91%)	0	Single suspicious node, largest or most malignant appearing sampled
van Rijk <i>et al.</i> ¹²	2006	FNAC	732	0	271 (37%)	58 (21%)	1	Suspicious nodes sampled. Not clear if single or multiple
Popli <i>et al.</i> ¹³	2006	FNAC	30	Not stated	22 (73%)	15 (68%)	0	Most accessible suspicious nodes, maximum number not stated
Nori <i>et al.</i> ⁴	2007	Core	132	0	42 (32%)	11 (26%)	0	Patients included only if at least 4 nodes visualised. 3 cores from each node sampled

Gilissen <i>et al.</i> ¹⁴	2008	FNAC	195	Not stated	93 (48%)	52 (56%)	0	Suspicious nodes sampled. Not clear if single or multiple
Alkuwari & Auger. ¹⁷	2008	FNAC	49	Not stated	Not stated	Not stated (63%)	0	Retrospective review of pathologic material
Current study	2009	FNAC	369 ^e	Not available	116 (31%)	38 (33%)	1	Single FNAC of most abnormal node

^a Figures include a small number of DCIS; 8 cases from reference ¹¹ and 3 cases from reference⁴.

^b In one paper² the nodes were described as 'suspicious for malignancy and in the other¹⁰ the figures refer to "palpable nodes". In this second paper, a lower figure (36) was quoted for 'suspicious nodes'.

^c Figures include micrometastases; from reference ⁶ 8 cases, reference ⁷ 34 cases, reference ¹¹ 17, reference ⁴ 20, reference¹⁴ 13 and current study 14 cases. Of these 106 cases, only 1 micrometastasis was identified pre-operatively⁷.

^d Figures include 6 patients who did not have axillary surgery as they were subsequently found to have metastatic disease.

^e Majority (n=287) screen-detected,