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Ultrasound-guided fine needle aspiration cytology of axillary lymph nodes in breast cancer patients. A preoperative staging procedure

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Abstract

Currently, axillary lymph node dissection is increasingly being replaced by the sentinel node procedure. This method is time-consuming and the full immunohistochemical evaluation is usually only first known postoperatively. This study was designed to evaluate the accuracy of preoperative ultrasound-guided fine needle aspirations (FNAs) for the detection of non-palpable lymph node metastases in primary breast cancer patients. We evaluated the material of 183 ultrasound-guided FNAs of non-palpable axillary lymph nodes of primary breast cancer patients. The cytological results were compared with the final histological diagnosis. Ultrasound-guided FNA detected metastases in 44% (37/85) of histologically node-positive patients, in 20% of the total patient population studied. These pecentages are likely to be higher when women with palpable nodes are included. Cytologically false-negative and false-positive nodes were seen in 28 (15%) and three cases (1.6%), respectively. Interestingly 25% ($n=7$) of the false-negative nodes, revealed micrometastases on postoperative histology. The sensitivity was 57%, the specificity 96%. We conclude that ultrasound-guided FNA of the axillary lymph nodes is an effective procedure that should be included in the preoperative staging of all primary breast cancer patients. Whether lymph nodes are palpable or not, it will save considerable operating time by selecting those who need a complete axillary lymph node dissection at primary surgery and would save a significant number of sentinel lymph node dissections (SLNDs).

Keywords: Breast cancer; Ultrasound; FNA; Lymph node; Axilla

1. Introduction

Lymph node status has long been the golden standard in determining the prognosis of breast cancer patients. Lately, the need for complete axillary dissection as a common staging procedure for all breast cancer patients has been questioned, because of the high morbidity of the procedure caused by lymphoedema and neuropathy of the involved arm. For this reason, regional lymph node staging by histological examination of the so-called sentinel node, defined as the first node draining the primary tumour in the regional lymphatic basin, has been introduced. Various studies [1–3] have now shown that histopathological examination of the sentinel node is reliable in predicting axillary lymph node status in breast cancer. Consequently, this procedure can replace routine axillary lymphadenectomy when the sentinel node is found to be negative. However, the procedure is time-consuming and the full histological and immunohistochemical evaluation is often only first known post-operatively. It would therefore be of great interest for

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the patient and surgeon to find an accurate technique for identifying lymph node metastases preoperatively.

Bonnema and colleagues [4] have studied the accuracy of ultrasonographically-guided fine needle aspiration (FNA) of non-palpable axillary lymph nodes in detecting breast cancer metastases. They found that ultrasound-guided FNA of the axilla could be performed in 62% of patients with primary breast cancer and that 63% of all node-positive patients could be detected preoperatively by this method. In a multicentre study of the sentinel node staging procedure, the preoperatively performed ultrasound-guided cytology showed a 36% detection rate of the lymph node metastases [5]. These results were promising and in our institute FNA cytology of non-palpable axillary lymph node under ultrasound guidance before primary surgery has become the standard procedure in the preoperative staging of primary breast cancer patients. Here, we present the outcome of our analysis of the cytology of axillary lymph nodes of breast cancer patients collected between January 1998 and July 2000.

2. Patients and methods

2.1. Patient material

Axillary lymph node material from 180 patients with a primary diagnosis of breast cancer was collected from January 1998 until July 2000. 3 patients had bilateral breast carcinomas and therefore FNAs of both left and right axillary nodes were performed. Thus, the final study consisted of material from 183 lymph nodes of 180 patients. Ultrasonographic evaluation of the axilla was carried out with an Acuson XP 128 (Acuson, Mountain View, CA, USA) using a 7.5-MHz linear array transducer. When lymph nodes were visible an ultrasound-guided FNA was performed with a 21-G needle, regardless of the benign/malignant ultrasound pattern. When more nodes were seen, either the sonographically most malignant looking, or the one closest to the breast and therefore most likely to be the sentinel node, was aspirated. The slides were Giemsa stained and evaluated according to the following three criteria: none or only few lymphocytes: inadequate; many lymphocytes, but no epithelial cells: benign; atypical epithelial cells in combination with lymphocytes: malignant. When atypical epithelial cells, but no lymphocytes were found and it was not apparent that an actual lymph node was aspirated, it was mentioned in the conclusion.

When the cytological diagnosis of the lymph node was positive, a complete axillary lymph node dissection was performed at primary surgery. In all other cases, a routine sentinel node procedure was applied as described in Ref. [5]. In short, the identification of the sentinel node was realised by peritumoral injection of 30–40 MBq ^{99m}Tc-radiolabelled nanocolloid at least 2.5 h before surgery and intradermal injection of 0.5 ml patent blue dye during the operation. The sentinel node was identified with the guidance of the RMD-CTC4 probe (Radiation Monitoring Devices, Watertown, ME, USA) and the blue- stained lymph vessel. Frozen sections of the sentinel node were examined and when negative, multiple at 250-μ intervals stepwise, sectioned paraffin slides were studied—following standard histological and immunohistochemical staining procedures using a monoclonal antibody against low molecular weight cytokeratin (CAM 5.2, Dako, Denmark) [6]. Histological features of the tumour were recorded. Typing was performed following the World Health Organization (WHO) classification, grading was done according to Bloom and Richardson [7].

The results were analysed with descriptive statistical methods. Sensitivity, specificity, overall accuracy, and positive and negative predictive values were calculated by comparing the results of FNAB and histological findings.

3. Results

The clinicopathological features of the primary breast cancers are listed in Table 1. The histological subtypes included 155 ductal, 12 lobular, 5 mixed and 11 other type carcinomas. Most tumours were grade II ($n=77$, 42%), pT1 ($n=131$, 72%) and N0 ($n=98$, 54%). There was only one pT3 tumour.

Table 2 gives the correlation between the cytological and histological diagnosis of the axillary nodes. In

Table 1
Pathological characteristics of 183 breast cancer specimens

	n	%
Type		
Ductal	155	(85)
Lobular	12	(7)
Mixed	5	(3)
Other	11	(6)
Grade		
I	43	(23)
II	77	(42)
III	60	(33)
Unknown	3	(2)
Size		
T1	131	(72)
T2	51	(28)
T3	1	(0.5)
N		
N0	98	(54)
N1–3	58	(32)
N > 3	24	(13)
Unknown	3	(2)

Table 2
Correlation between cytological and histological diagnoses

Cytology	Histology		
	n	Benign	Malignant
Inadequate	49	29	20
Benign	94	66	28
Malignant	40	3	37
Total	183	98	85

49/183 (27%) cases, insufficient material was aspirated, 20 of which were histologically-positive. In 103/183 (56%), the cytology and histology was concordant, i.e. 37/103 were both positive for malignancy and 66/103 were both negative for malignancy. In 31/183 (17%) lymph nodes, the cytological and histological results did not correspond: in 28 cytologically-negative cases, histologically-positive lymph nodes were seen. However, histology of three cytologically-positive nodes (1.6%) did not reveal cancer metastases. Reviewing the cytology of the latter lymph nodes, we found that the material presented as lymph node aspiration in one case did show tumour cells against a background of lymphocytes and was in our opinion therefore rightly considered to be a metastasis. However, histology showed that the primary tumour was multifocal and the more laterally located small tumour area in particular was surrounded by lymphocytes. This lateral tumour extension was considered a likely explanation for the positive cytology result. In the next case at second look, the aspirated cell groups, misread as metastatic groups, were interpreted as mesothelial cells. Apparently, the radiologist had aspirated material from the pleural cavity. In the last case, tumour groups but no lymphocytes were seen in the cytological specimen, but since the consulted radiologist confirmed that an axillary lesion was aspirated, it was considered to be a lymph node metastasis. Nevertheless, no positive nodes were found in the surgical specimen.

Most inadequate and false-negative aspirations were found in the group with one positive node, 13 and 17, respectively (Table 3). Of these 17 false-negative aspirations, seven contained micrometastases only, i.e. 25% (7/28) of the total number of cytologically false-negative nodes.

Of the total group with one histologically-positive node, 25% was cytologically-detected, compared with 83% in the group with more than three positive nodes. Three patients with a positive sentinel node refused further surgery and, consequently, no axillary dissection was performed and the number of positive nodes is unknown. In those cases, regular ultrasound examinations of the axilla were included in the follow-up.

The relationship between the size of the tumour, the number of histologically-positive nodes and cytological detection, is shown in Table 4. In 29% (14/49) of T1 tumours and and in 64% (23/36) of T2 tumours histologically-positive nodes were cytologically-detected, in 57% (13/23) of T2 tumours with more than three positive nodes.

In 20% of the total patient population studied, lymph node metastases were cytologically-detected. This is 44% (37/85) of the group of patients with histologically-proven positive lymph nodes.

The sensitivity (the aspirations with inadequate material not included) was 57%, the specificity 96%, overall accuracy 76% and positive and negative predictive values 92%, and 70%, respectively.

4. Discussion

A simple reliable preoperative assessment of the axillary lymph node status of primary breast cancer patients would be of great value for the patient and surgeon, especially since the introduction of the sentinel node procedure. It would save time and costs by avoiding this procedure when metastases are found. Non-palpable axillary lymph nodes can be detected by ultrasound. Unfortunately, the accuracy of ultrasonography is too low to rely on this technique for the selection of

Table 3
Correlation between cytological diagnosis and lymph node status

	Number of histologically-positive lymph nodes					
Cyt	$n=1$	$n=2$–3	$n=>3$	Unknown	Total (%)	
Inadequate	13 (5[a])	4	1	2 (1[a])	20	(24)
Benign	17 (7[a])	7	3	1	28	(33)
Malignant	10	7	20	–	37	(44)
Total	40	18	24	3	85	

[a] Number of lymph nodes with only micrometastases.

Table 4
Correlation between tumour size and number of histologically-positive lymph nodes (number of cytologically-detected nodes between parentheses)

	$N=1$	$N=2$–3	$N=>3$	N?	Total (%)
T1					
1a	1	–	1	–	2
1b	8 (1)	1 (1)	–	–	9 (2)
1c	20 (3)	7 (2)	9 (7)	2[a]	38 (12)
T2	11 (6)	10 (4)	14 (13)	1[a]	36 (23)
Total	40 (10)	18 (7)	24 (20)	3	85 (37)

[a] 3 patients with a positive sentinel node, refused further surgery and therefore the number of positive nodes is not known.

node-negative/positive patients, the sensitivity being 36–73% and the specificity between 70 and 100% [4,5,8–10]. A combined approach of ultrasound and FNA cytology is rarely applied [4,5,11], but the results are promising. Bonnema and colleagues [4] found that in 87% of ultrasound-guided FNA of axillary lymph nodes, adequate material was aspirated, with a sensitivity and specificity of 63 and 100%, respectively. In the study of Kanter and colleagues [5], the sensitivity was 36% and the specificity 100%. We found that 73% of lymph node aspirations contained adequate material with a sensitivity of 57% and a specificity of 96%. These variations in the detection of metastases may be explained by the fact that in Bonnema's study two experienced radiologists were involved whereas in the other two studies, several radiologists did the aspirations and some of them had little experience with this technique. However, after a learning phase, the identification and aspiration of lymph nodes improved and so did the results (data not shown). It underlines the importance of good communication between the radiologist, pathologist and surgeon to maintain high standards with regard to the quality of the proceedings.

Unfortunately, 3 cases of positive cytology proved to be negative in histology. In 1 case this could be explained by the multifocality of the tumour, associated with a dense lymphocytic infiltrate. It is known that in multifocal breast cancer, a negative sentinel node does not exclude axillary metastases [12]. Therefore, a complete axillary lymph node dissection has to be performed. The second false-positive case was caused by cytological misreading of the cell groups. Here, a complete lymph node dissection was an overtreatment. Awareness of the rare possibility that the pleural cavity is aspirated may help to avoid this pitfall. The third case remains unexplained.

Cytologically false-negative and inadequate findings were in general restricted to the group of patients with one or 2–3 positive nodes. That so few lymph nodes are positive may explain why aspiration is more difficult and the chance of sampling errors is enhanced. What is even more important, 25% of the cytologically false-negative lymph nodes, were found histologically to contain micrometastases only. Although the biological significance of these micrometastases is still being discussed, it is clear that neither ultrasound nor cytology can replace histology in the detection of these metastases, but it partly explains the relative low sensitivity (57%) found in this study.

Screening programmes have led to an earlier diagnosis of breast cancer and therefore smaller invasive cancers [13]. Moreover, the size of the tumour is related to the number of nodes involved [14–16]. Consistent with these findings, we observed that 131/183 (72%) of the tumours were T1. However, the percentage of T1 tumours with positive nodes was relatively high (37%) compared with other studies [16–18]. Most likely a selection bias has occurred. After all, patients were selected upon the sonographical visibility of the axillary lymph nodes and since metastic lymph nodes are in principal visible, the chance of nodes being positive was much higher in this group than in a population of primary breast cancer patients with no visible nodes.

In this study, ultrasound-guided FNA could identify 44% of histologically-proven axillary metastases in primary breast cancer patients with pT1 and pT2 tumours, 20% of the total patient population. Consequently, the sentinel node procedure could be avoided, saving considerable operating time as the surgeon can proceed to axillary dissection without waiting for frozen sections and avoiding a second operation later.

Both ultrasound and FNA are non-aggressive, patient-friendly and reliable methods, relatively easy to apply when in experienced hands. We conclude that ultrasound-guided FNA of the axilla should be included in the preoperative staging procedure of all primary breast cancer patients. It it will save a significant number of SLNDs, by selecting those patients who need a total axillary lymph node dissection at primary surgery.

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