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Fine Needle Aspiration and Tru-Cut Biopsy in the Diagnosis of Soft Tissue Metastases in Breast Cancer

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Abstract—*Soft tissue is a common site of the first recurrence in patients with breast cancer, and soft tissue lesions are often used to assess the efficacy of systemic therapy. It is therefore desirable to obtain histological/cytological verification of such lesions. It is our experience that FNA and TCB in psycho-social respects are superior to a surgical biopsy. Using a surgical biopsy as the key-diagnosis we have compared the diagnostic value of Fine-Needle Aspiration (FNA), Tru-Cut Biopsy (TCB) and clinical evaluation. The FNA was found to be significantly better than TCB in establishing the diagnosis. The diagnostic specificity and sensitivity for FNA was* 1.0 *and* 0.65, *while the corresponding figures for TCB and the clinical diagnosis were* 1.0 *and* 0.36 *and* 0.76 *and* 0.33, *respectively. Since no false positive results were obtained by use of FNA, this procedure seems to be a sufficient diagnostic procedure. However, in case of a negative outcome of the FNA, the diagnosis must be obtained by a surgical biopsy.*

INTRODUCTION

FIRST RECURRENCE in patients with breast cancer is most frequently localized in soft tissue [1]. Moreover, soft tissue metastases are often used as measurable lesions for the evaluation of efficacy of cytotoxic or endocrine therapy in the treatment of advanced breast cancer. Therefore, it is desirable to obtain a histological verification of such lesions. The most used and accepted method is the surgical biopsy. Alternative methods are Fine-Needle Aspiration (FNA) and Tru-Cut Biopsy (TCB). FNA and TCB are relatively atraumatic to the patient and can be performed in the out-patient clinic by the oncologist, at the time when the soft tissue tumour is recognized. The surgical biopsy, on the other hand, has to be performed in the surgical ward. FNA and TCB are thus superior to the surgical biopsy in psycho- and socio-economic respects, in being time saving, physically and psychically more gentle to the patient, and also cheaper. Moreover, the measurable lesion can be left in order to evaluate the efficacy of the treatment. Furthermore, since techniques are now available for the measurment of estrogen receptors and DNA content in small samples of tissue [2–6], it is important to examine the accuracy of the different tools that can be used to obtain tumour cells from soft tissue lesions. Fine-Needle Aspiration (FNA) and Tru-Cut Biopsy (TCB) are approved methods for establishing the preoperative diagnosis of breast lumps. Both procedures have been examined in several studies that report varying degrees of statistical efficacy [7–9]. There are, however, only a few reports concerning the value of FNA as a diagnostic tool in the diagnosis of soft tissue metastases [10, 11], and we have found no reports of TCB in this regard. In the present study, use of FNA and TCB for the diagnosis of soft tissue recurrences in patients with breast cancer will be compared.

METHODS

Patients with a primary diagnosis of breast cancer and with a lesion in soft tissue that was more than 0.5 cm in size were included in this study. In the out-patient clinic the patients were clinically evaluated as having a benign, a suspicious, or a malignant lesion. Thereafter, FNA and TCB were performed by two of us. A subsequent surgical biopsy served as the key-diagnosis. After local analgesia the FNA was performed as recommended by Zajicek [10] and Frable [11, 12] with three minor

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exceptions. Zajicek and Frable both used a 20–22 gauge thin-walled needle with an external diameter of about 0.6 mm. We have used an even thinner needle, a 25 guage needle (0.5 × 25 mm). Before entering the needle into the tumour, we withdrew the piston of the syringe to the 1 ml mark. The air in the syringe was later used to expel the sample on to a glass slide (the same procedure has been used by J.E. Russ *et al.* [26] in FNA of primary breast tumours). A smear was made with the needle.

The TCB was performed with a Pistomate (Fig. 1, bottom) as recommended by Nielsen and Blichert Toft [13]. In brief, the skin over the tumour was incised with a scalpel, whereafter the tumour was grasped with the free hand and the Tru-cut needle with the obturator covering the specimen notch was inserted through the subcutis to the tumour. The Tru-cut needle (without the obturator) was then inserted into the tumour with the thumb of the right hand, whereby the specimen notch was opened. The trigger of the Pistomate was released, and the specimen notch cut a biopsy of the tumour.

The patients were then referred to the surgical ward for a surgical biopsy. The smears for cytology were air-dried and fixed in methanol for 5 min. The TCB and the surgical biopsies were fixed in formalin buffer. The cytologic smears were stained with Giemsa and the histological biopsies with Haematoxiline–Eosine and Van Gieson-Hansen + Alcian blue (pH 2.7). The specimens were examined by a single pathologist who classified the smears, the Tru-cut biopsies and the surgical biopsies independently. The specimens were classifed into one of four diagnostic categories; positive (malignant cells/tissue present), suspicious (cells/-tissue suspicious of malignancy present), negative (only benign cells/tissue present), or unsatisfactory for evaluation.

The study was performed in accordance with the Helsinki Declaration II of 1975, and the patients were informed both orally and in writing.

STATISTICAL METHODS

Different methods of describing the statistical efficacy of diagnostic tests can be used. The indexes are usually calculated from the arrangement shown in Table 1. Each index has a maximum value of 1.00 (100%). Most often, the indirect or nosological probabilities are stated. They express the probability that a patient presents or does not present with a positive test, when the disease is present or absent. However, the diagnostic probabilities seem more relevant to the clinician, since they state the probability of presence or absence of the disease, given a positive or negative test. In this study each test is described by its diagnostic specificity, diagnostic sensitivity, and diagnostic accuracy. The diagnostic specificity states the probability of recurrence in case of a positive test. Correspondingly, the diagnostic sensitivity indicates the probability that a patient does not have recurrent disease, provided that the test is negative [14]. Alternative designations of diagnostic specificity and sensitivity are accuracy of positive prediction and accuracy of negative prediction [15]. Finally we evaluated the diagnostic accuracy, which expresses the combined positive and negative accuracy of a test. Using the symbols in Table 1 we have:

$$\text{Diagnostic specificity: } \frac{a}{(a+b)} = \frac{\text{True Positive}}{\text{All Positive}}$$

$$\text{Diagnostic sensitivity: } \frac{d}{(c+d)} = \frac{\text{True Negative}}{\text{All Negative}}$$

$$\text{Diagnostic accuracy: } \frac{a+d}{N} = \frac{\text{True Positive} + \text{True Negative}}{\text{Total number of test}}$$

The diagnostic tests are compared using the Sign-test and Mc-Nemar-test (paired design) [16]. The diagnostic gain is evaluated by comparing the most accurate of the diagnostic tests with each other. The diagnostic gain is defined as:

$$\frac{P_1 - P_2}{N} \pm 1.96 \sqrt{\frac{P_1 + P_2}{N}} \text{ (95\% confidence limits)}$$

[16]. P_1 and P_2 express the preferences for the tests.

RESULTS

Fifty-eight consecutive patients were included in the study. A surgical biopsy could be obtained in only 52 of the 58 patients. One of the 52 patients had to be excluded since the biopsied tumour was a primary breast cancer. One patient had two tumours; thus, 52 specimens of both FNA, TCB, and a surgical biopsy were available for study. The characteristics for the patients and their tumours are shown in Tables 2 and 3. The results of the diagnostic tests are presented in Table 4. The surgical biopsy was malignant in 75% of the tumours. In Table 5, the key-diagnosis is compared to the clinical diagnosis, FNA, and TCB. There were no false positive tests for FNA and TCB, while 23% of the clinical diagnoses were false positive. Forty-four per cent of the TCB, 13% of the FNA, and 4% of the clinical diagnoses were false negative. Six of the seven negative FNA were localized in the ipsilateral axilla (24% of tumours in ipsilateral axilla), and one in the contralateral breast (33%). Median tumour diameter was 30 mm with a range from 10 to 55 mm. Regarding

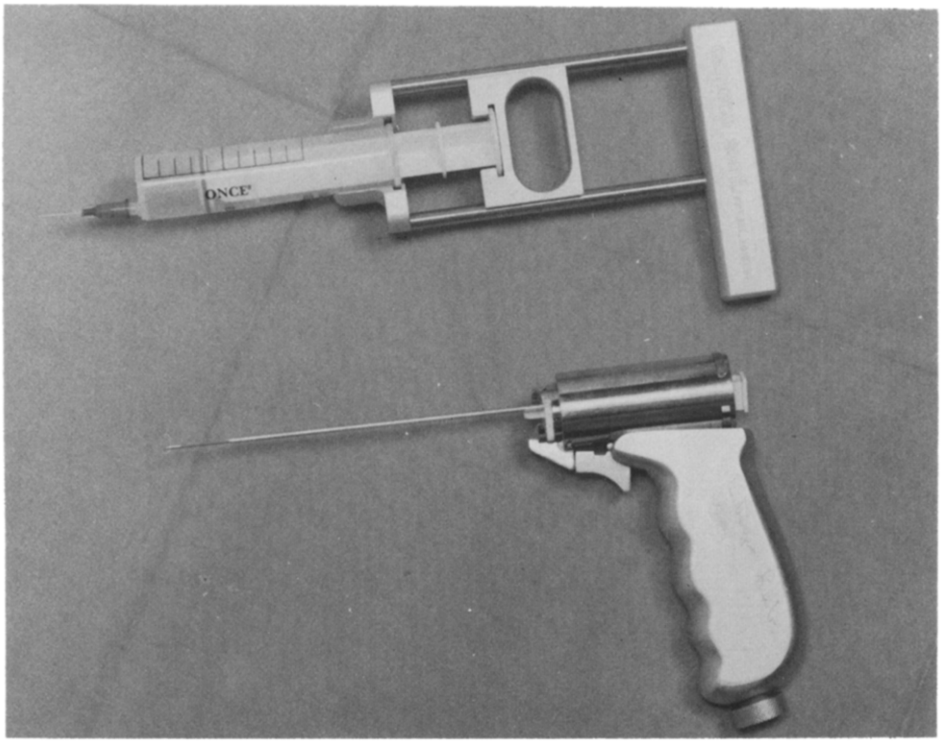

Fig. 1. Handle with adapted syringe and needle for Fine-Needle Aspiration (top) and Pistomate with adapted Tru-Cut Biopsy needle (bottom).

Table 1. *Results of diagnostic tests*

Test result	State of disease		
	Present	Absent	Total
Positive	*a*	*b*	*a+b*
Negative	*c*	*d*	*c+d*
Total	*a+c*	*b+d*	N

Table 2. *Patient characteristics*

Age (yr) at biopsy, n = 51
Median : 64
Range : 35–78

Disease-free interval (months), n = 38 (13 *benign*)
Median : 26
Range : 0–211

Menopausal status
Pre/peri-menopausal : 10
Post-menopausal : 41

Relapse number, n = 38 (13 *benign*)
1. relapse : 22 patients
2.–3. relapse : 15 patients
> 3. relapse : 1 patient

Table 3. *Tumour characteristics*

Tumour diameter (mm), (n = 52)
Median : 30
Range : 6–100

Localisation of biopsed tumour, (n = 52)
Local : 17
Ipsilateral axilla : 25
Contralateral axilla : 4
Contralateral breast : 3
Elsewhere : 3

Prior radiotherapy in the tumour region
Benign tumours : 6
Malignant tumours : 10

the false negative TCB, 13 were in the ipsilateral axilla (52% of tumours in ipsilateral axilla), one in contralateral axilla (25%), eight local (47% of local tumours), and one in contralateral breast (33%). Median tumour diameter was 25 mm with a range from 6 to 55 mm. When the excisional biopsy serves as the key-diagnosis, the diagnostic probabilities of the clinical diagnosis, FNA, and TCB can be seen in Table 6. The diagnostic specificity for FNA and TCB is 1.00. In contrast, the diagnostic specificity for the clinical diagnosis is only 0.76. The diagnostic sensitivity is highest for FNA (0.65) while it is 0.36 and 0.33 for TCB and clinical diagnosis, respectively. Similarly, the diagnostic accuracy is highest for FNA (0.87), while the accuracy for the clinical diagnosis and TCB is 0.73 and 0.56. In Table 7a FNA is compared directly to TCB. In 17 cases, FNA was better than TCB, while TCB was better than FNA in only one case. The two tests were equal in 34 cases (65%). With 17 preferences for FNA and one for TCB, the Sign-test and Mc-Nemar-test show that the FNA is significantly better than TCB in establishing the diagnosis of soft tissue metastasis in breast cancer ($P = 0.0004$). The diagnostic gain obtained by use of FNA instead of TCB is 15–47% (95% C.L.). When comparing FNA and the clinical diagnosis (Table 7b) the two tests were equal in 33 cases. FNA was superior to the clinical diagnosis in 13 cases, while the clinical diagnosis was superior in six cases. However, by applying the Sign-test and the Mc-Nemar-test to these figures, it appears that the trend in favour of FNA is not significant ($P = 0.17$).

DISCUSSION

By clinical evaluation of soft tissue tumours in patients with a history of breast cancer, we have found a diagnostic specificity of 0.76 with 95% confidence limits from 0.62 to 0.87. This means that there will be a 62–87% probability that the soft tissue tumour is histologically malignant when the clinician considers the lesion to be malignant/suspicious. This implies an overtreatment of 13–38% of the patients if the clinical diagnosis was the only diagnosis relied upon. The sensitivity of the clinical diagnosis is low in our study (0.33; 95% C.L: 0.01–0.91). It is, however, difficult to draw any conclusions from this calculation, since only three tumours were clinically evaluated as most likely being benign. In view of the serious

Table 4. *Results of the diagnostic tests*

	Clinical diagnosis		Fine-Needle		Tru-cut		Excisional biopsy	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Positive/ malignant	26	(50)	27	(52)	15	(29)	39	(75)
Suspicious	23	(44)	5	(10)	1	(2)	–	
Negative/ benign	3	(6)	20	(38)	36	(69)	13	(25

Table 5. Preoperative evaluation compared to the result of the surgical biopsy in 52 tumours

	True positive* (histologically malignant)		False positive* (histologically benign)		False negative† (histologically malignant)		True negative† (histologically benign)	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Clinical diagnosis	37	(71)	12	(23)	2	(4)	1	(2)
Fine-Needle Aspiration	32	(62)	0	(0)	7	(13)	13	(25)
Tru-Cut Biopsy	16	(31)	0	(0)	23	(44)	13	(25)

*Positive tests of FNA and TCB include tumour cells and cells suspicious of malignancy.
†Negative tests include unsatisfactory specimens.

Table 6. Diagnostic probabilities and accuracy of FNA and TCB in 52 tumours

	Diagnostic specificity	Diagnostic sensitivity	Diagnostic accuracy
Clinical diagnosis	0.76 (0.62–0.87)	0.33 (0.01–0.91)	0.73 (0.59–0.84)
Fine-Needle Aspiration	1.0 (0.89–1)	0.65 (0.40–0.85)	0.87 (0.74–0.94)
Tru-cut Biopsy	1.0 (0.80–1)	0.36 (0.21–0.54)	0.56 (0.41–0.70)

*95% Confidence limits are given in parenthesis.

Table 7a. Fine-needle aspiration compared to Tru-Cut Biopsy

		FNA		
		True tests	False tests	Total
TCB	True tests	28 (54)	1 (2)	29 (56)
	False tests	17 (33)	6 (11)	23 (44)
	Total	45 (87)	7 (13)	52 (100)

*Per cents are given in parenthesis.
FNA significantly better than TCB (Sign-test and Mc-Nemar-test; $P = 0.0004$)
Diagnostic gain by applying FNA instead of TCB: 15–47% (95% C.L.)

Table 7b. Fine-needle aspiration compared to clinical diagnosis

		FNA		
		True tests	False tests	Total
Clinical diagnosis	True tests	32 (62)	6 (12)	38 (73)
	False tests	13 (25)	1 (2)	14 (27)
Total		45 (87)	7 (14)	52 (100)

*Per cents are given in parenthesis.
There is no significant difference between FNA and clinical diagnosis (Sign-test and Mc-Nemar-test; $P = 0.17$).

implications of the initiation of systemic therapy for recurrent breast cancer, we must search for diagnostic methods with high specificity and sensitivity. In our study the diagnostic specificities of both FNA and TCB are high (1.0), which implies that a positive FNA or TCB is a reliable indicator of malignant disease. Since the diagnostic sensitivity for FNA is higher than that for TCB, there seems to be a greater possibility for a tumour to be histologically benign when the FNA is negative, than when TCB is negative. Although we could not find any significant difference between the clinical diagnosis and FNA in establishing the diagnosis of soft tissue metastasis, comparing them with the Sign-test and Mc-Nemar-test, the latter seems to be an indispensable supplement to the clinical diagnosis because of its higher diagnostic specificity. However, it is noteworthy that there is a considerable risk that a negative FNA will indicate a false negative test, since the proportion of a false negative test-result is 0.35 (94% C.L. 0.15–0.59). This proportion might be reduced by performing more than one aspiration from the same soft tissue lesion [7]. In this regard it must be noticed that 86% of the false negative FNA were localized in the ipsilateral axilla, constituting 24% of the tumours in the ipsilateral axilla. Special caution must thus be exercised with FNA from tumours in the axillae. In contrast, FNA seems to be very safe with local tumours. Diameter of the tumour does not seem to influence the result of our study, probably reflecting that the small palpable tumours are located superficially. No special localization was noticed for the false negative TCB. FNA has been applied to soft tissue tumours in two other studies. In order to compare these studies with the present study we have, whenever possible, converted their figures of nosologic probabilities to diagnostic probabilities. In 1976 Frable [11] reported on the use of FNA in 173 lymph nodes and found a diagnostic specificity of 1.00 and a diagnostic sensitivity of 0.87. Zajicek [10] published the results of FNA in 461 lymph node metastases. A surgical biopsy served as the key-diagnosis. From the data given it is only possible to estimate the nosological sensitivity (0.93).

The efficacy of FNA has been evaluated in several studies of primary breast lumps in recent years. The diagnostic specificities have varied from 0.65 to 1.0 and the diagnostic sensitivities have varied from 0.90 to 1.0 [17–32, 10–12]. Correspondingly, the applicability of TCB as a diagnostic tool has been examined in seven studies [7–9, 13, 33–35]. From the pooled data there seems to be a trend toward slightly higher diagnostic specificities and lower diagnostic sensitivities with TCB compared to FNA. However, of three direct comparisons in primary breast lumps two studies conclude that FNA procedure is the most acurate procedure, whereas the third study found TCB to be superior [7–9].

It seems that the diagnostic specificities are higher for FNA in soft tissue lesions than those obtained in primary breast lumps. This is probably due to the fact that the differential diagnosis is less difficult in soft tissue metastases.

In conclusion, a clinical suspicion of a soft tissue metastasis in breast cancer must be validated by a cytological or histological diagnosis. In this regard, FNA and TCB are in our experience psychologically and socioeconomically superior to surgical biopsy. In our study, FNA is found to be significantly better than TCB. No false positive results are obtained by the use of FNA, but in the case of a negative outcome of the FNA procedure, an exact diagnosis must be obtained by surgical biopsy.

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