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Improvement in Early Detection of Breast Cancer by Combining Aspiration Biopsy Cytology and Xeromammography

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ABSTRACT

Accuracy and problems in diagnosis of breast tumors, especially those not more than 2.0 cm in diameter, were reviewed for 157 patients with breast tumors (94 primary cancer and 63 benign). They were diagnosed by aspiration biopsy cytology and xeromammography at their first examinations at our clinic from the end of October 1981 to the end of December 1985. The efficiency by aspiration biopsy cytology was 93.0% and that by xeromammography was 83.4%. The efficiency for the concurrent use of both methods was 96.8%. For small breast cancers not more than 1.0 cm and scirrhous cancers, the detection rate by either method was slightly lower but not significantly different. Aspiration biopsy cytology, in particular, showed a detection rate as high as 96.6% for those tumors more than 2.0 cm.

Recently, a number of attempts have been made to improve the early detection and diagnosis of breast cancer. It is clinically easier to detect abnormalities in the mammary gland located on the body surface than in other organs. However, for non-invasive (Tis), non-palpable (To) and relatively small cancers, accurate diagnosis may be difficult in many cases[4,17]. However, the fact that the disease-free and the survival rates of patients with early breast cancer are very high[2] has encouraged us to develop auxiliary diagnostic methods for the early detection of breast cancer. Efforts are being made for early detection on out-patients of tumors of the mammary glands at our clinic by using various combinations of every auxiliary diagnostic method available[11]. Since the end of October 1981 when aspiration biopsy cytology was first introduced to our clinic, it has been used on our out-patients suspected of having breast cancer. This paper describes the significance and problems with the concurrent use of aspiration biopsy cytology and xeromammography especially in breast cancer cases with small tumors not more than 2.0 cm in diameter.

MATERIALS AND METHODS

A comparison study was made between patients with benign or malignant breast disease during the period from the end of October 1981 to the end of December 1985. Of the 107 cases having been diagnosed and treated for primary breast cancer at our clinic, 94 cases had both aspiration biopsy cytology and xeromammography and formed one group. The other group of 63 cases included patients proved to have benign disease as diagnosed histopathologically by open biopsy after both aspiration biopsy cytology and xeromammography were performed during the same period. The average age of the 94 breast cancer cases was 51.2 ± 12.1 (M ± SD) including 41 premenopause and 53 postmenopause cases. They were classified by the location of tumor as 38 inner (or median) half and 56 out-

er half cases. By the histopathology[9], they included 5 non-invasive cancers, and 89 invasive cancers consisting of 16 papillo-tubular cancers, 45 solid-tubular cancers, 20 scirrhous cancers and 8 special types. Of the total, the cases with tumors not more than 2.0 cm in greatest dimension included 35 of breast cancer (37.2%) and 48 of benign disease (76.2%). Of these, the average age of the 35 cases of breast cancer less than 2.0 cm was 52.2 ± 10.6, including 2 cases of tumor 0.5 cm or less in its greatest dimension, 6 of 0.6—1.0 cm, 11 of 1.1—1.5 cm and 16 of 1.6—2.0 cm. Histologically, they included 4 non-invasive cancers (80% of the total number of non-invasive cancers) and 31 invasive cancers that included 5 papillo-tubular cancers (31.4%), 15 solid-tubular cancers (33.3%), 6 scirrhous cancers (30%) and 5 special types (62.5%).

The average age of the 63 cases of benign disease was 38.6 + 11.9, including one male. Histologically, they included 1 case of intraductal papilloma, 25 fibroadenomas, 30 mastopathies, 2 duct ectasias, 1 cystosarcoma phyllodes, 2 mastites, 1 gynecomastia and 1 accessory mammary gland. Of these, the average age of the 48 cases of tumor 2.0 cm or less in diameter was 37.9 ± 11.0, including 4 cases not more than 0.5 cm, 15 of 0.6—1.0 cm, 17 of 1.1—1.5 cm, and 12 of 1.6—2.0 cm. Histologically, they included 19 fibroadenomas, 23 mastopathies, 1 cystosarcoma phyllodes, 2 mastites, 2 duct ectasias and 1 accessory mammary gland.

Aspiration biopsy cytology was performed using a 10 ml disposable-syringe held in a syringe-pistol-holder (Cameco, Sweden) with a fine needle of 23 gauge. For smears, the May-Grünwald-Giemsa (M.G.G.) stain was used[13]. Of the breast cancer cases, those of cancer or suspicious of cancer diagnosed by cytology were taken as true positive and those diagnosed as benign disease or inadequate specimens, as false negative. Of the benign disease cases, those of benign disease by cytology were determined as true negative and those called cancer or suspicious of cancer, as false positive.

Xeromammography was performed with the "XEROX 125 SYSTEM" of Xerox Co. (U.S.A.)[19]. In diagnosing breast lesions, the malignant tumor signs were looked for. The cases showing a dark tumor shadow and irregular margin (including spiculation signs) or microcalcification were taken as positive mammograms, and those showing none of both, as negative cases. In this group of cases, indirect signs such as skin retraction were not observed. The parenchymal patterns were determined according to the J.N.Wolfe's classification[21].

RESULTS

The accuracy of detection of 94 breast cancer cases and 63 benign disease cases by aspiration biopsy cytology and xeromammography is as shown in Table 1. Aspiration biopsy cytology showed 91.5% sensitivity, 95.2% specificity and 93.0% efficiency, while xeromammography showed 81.9%, 85.7% and 83.4%, respectively. The detection rate by age for breast cancer by aspiration biopsy cytology (Table 2) showed a

Table 1. Accuracy of Aspiration Biopsy Cytology and Xeromammography

Diagnosis	Aspiration biopsy cytology (%)	Xeromammography (%)	Combination (%)
True positive	91.5 (86/94)	81.9 (77/94)	96.8 (91/94)
False negative	8.5 (8/94)	18.1 (17/94)	3.2 (3/94)
True negative	95.2 (60/63)	85.7 (54/63)	100 (63/63)
False positive	4.8 (3/63)	14.3 (9/63)	0 (0/63)

Aspiration biopsy cytology : sensitivity 91.5% $\left(\frac{TP}{TP + FN}\right)$

specificity 95.2% $\left(\frac{TN}{TN + FP}\right)$

efficiency 93.0% $\left(\frac{TP + TN}{Total}\right)$

Xeromammography : sensitivity 81.9%

specificity 85.7%

efficiency 83.4%

lower rate for younger cases but was not a significant difference, while that by xeromammography showed no definite trend. The detection rate classified by location was somewhat lower for outer half tumors by aspiration biopsy cytology and inner (or median) half tumors by xeromammography was somewhat lower, but were not significantly different (Table 3). Table 4 shows the detection rate classified by size of tumor for aspiration biopsy cytology. That is, the detection rate was 62.5% for primary breast cancer not more than 1.0 cm, 88.9% for that of 1.1—2.0 cm, and 96.6% for that not less than 2.1 cm. Of the benign disease cases, only 3 cases (2 fibrocystic diseases and 1 sclerosing adenosis) were misdiagnosed as cancer. The efficiency was 76.9% for tumors 1.0 cm or less, 96.5% for 1.1—2.0 cm tumors and 97.3% for 2.1 cm or larger.

The difference was statistically significant be-

Table 2. Detection of Breast Cancer according to Age

Age (Yr)	Aspiration biopsy cytology (%)	Xeromammography (%)
— 40	85 (17/20)	85 (17/20)
40 — 49	90.9 (20/22)	77.3 (17/22)
50 — 59	90.3 (28/31)	74.2 (23/31)
60 —	100 (21/21)	95.2 (20/21)

No significant difference between age groups for either technique

Table 3. Detection of Breast Cancer according to Location of Tumor

Location of tumor	Aspiration biopsy cytology (%)	Xeromammography (%)
Inner half	92.1 (35/38)	81.6 (31/38)
Outer half	91.1 (51/56)	82.1 (46/56)

No significant difference between both inner and outer half by either technique

Table 4. Detection of Breast Tumors by Aspiration Biopsy Cytology according to Tumor Diameter

Tumos diameter (cm)	Breast cancer % (No.)	Benign disease % (No.)	Total cases % (No.)
— 1.0	62.5 (5/8)	83.3 (15/18)	76.9 (20/26)[a]
1.1 — 2.0	88.9 (24/27)	100 (30/30)	96.5 (55/57)[b]
— 2.0	82.9 (29/35)	93.8 (45/48)	90.4 (75/83)[c]
2.1 —	96.6 (57/59)	100 (15/15)	97.3 (72/74)[d]

* Significant difference between a and b ($p<0.01$; $X^2 = 8.26$)
** No significant difference between c and d ($X^2 = 2.10$)

Table 5. Detection of Breast Cancer by Aspiration Biopsy Cytology according to the Histological Type

Histological type	Tumor diameter		Total cases % (No.)
	— 2.0 cm (%)	2.1 — cm (%)	
Non-invasive cancer	75 (3/4)	100 (1/1)	80 (4/5)
Papillotubular ca.	100 (5/5)	90.9 (10/11)	93.8 (15/16)
Solid-tubular ca.	93.3 (14/15)	96.7 (29/30)	95.6 (43/45)
Scirrhous ca.	83.3 (5/6)	85.7 (12/14)	85 (17/20)
Special type	80 (4/5)	100 (3/3)	87.5 (7/8)

No significant difference between groups

Table 6. Detection of Breast Tumors by Xeromammography according to Tumor Diameter

Tumor diameter (cm)	Breast cancer % (No.)	Benign disease % (No.)	Total cases % (No.)
— 1.0	62.5 (5/8)	83.3 (15/18)	76.9 (20/26)[a]
1.1 — 2.0	77.8 (21/27)	90 (27/30)	84.2 (48/57)[b]
— 2.0	74.3 (26/35)	87.5 (42/48)	81.9 (68/83)[c]
2.1 —	86.4 (51/59)	80 (12/15)	85.1 (63/74)[d]

No significant difference among a,b,c and d

Table 7. Detection of Breast Cancer by Xeromammography according to Histological Type

Histological type	Tumor diameter		Total (%)
	— 2.0 cm (%)	2.1 — cm (%)	
Non-invasive ca.	100 (4/4)	100 (1/1)	100 (5/5)
Papillotubular ca.	100 (5/5)	100 (11/11)	100 (16/16)
Solid-tubular ca.	73.3 (11/15)	80 (24/30)	77.8 (35/45)
Scirrhous ca.	50 (3/6)	78.6 (11/14)	70 (14/20)
Special type	80 (4/5)	100 (3/3)	87.5 (7/8)

No significant difference between groups

Table 8. Prevalance of Breast Disease according to Parenchymal Pattern by Xeromammography

Disease	Parenchymal pattern		
	Nl + Pl (No.)	P2 + DY (No.)	P2 + DY/Total (%)
Breast cancer	38	56	59.6 (56/94)[a]
Benign disease	39	24	38.1 (24/63)[b]

Significant difference between a and b ($p<0.01$; $X^2 = 6.96$)

tween those 1.0 cm or less and those greater than 1.0 cm ($p<0.01$). The detection rate classified by histological type of breast cancer for aspiration biopsy cytology was as low as 80% for all the non-invasive cancer and 85% for all scirrhous cancer (Table 5). The detection rate classified by size of tumor for xeromammography is shown in Table 6. The cases of primary breast cancer showed a relatively true correlation between the tumor size and percent detection. The cases of benign disease showed no definite trend. The detection rate classified by histological type was lower for scirrhous cancer and solid-tubular cancer (Table 7). The frequency of direct malignant signs for primary breast cancer was 68.1% for dark tumor shadow with irregular margin and 37.2% for microcalcification, and for mastopathy was 16.7% and 16.7%, respectively, and for fibroadenoma was 28% and 16%, respectively. The frequency of direct malignant signs classified by parenchymal pattern by xeromammography showed many cases of breast cancer ($p<0.01$) in the high risk (P2 + DY) groups (Table 8).

DISCUSSION

It is essential for early detection and diagnosis of breast cancer to make progress and improvement in early breast cancer diagnosis techniques as well as to popularize the breast self-examination (B.S.E.) and its practice. In general, surgeons using the "Breast Cancer TNM Classification" proposed by the UICC define early breast cancer as including tumors not more than 2.0 cm in their greatest dimension with non-palpable homolateral axillary lymph nodes (Tl, Stage I); non-palpable cancer (To); and non-invasive cancer (Tis). Many other reports call non-invasive and invasive cancer with a tumor not more than 0.5 cm in its greatest dimension as "Minimal Breast Cancer"[8] which is defined as true early breast cancer[4,20] because of its very good prognosis. The purpose of studies of various auxiliary breast cancer diagnostic methods is to find early breast cancer of good prognosis and diagnose them as such at the earliest possible time. The role to be played by aspiration biopsy cytology and xeromammography in early diagnosis of early breast cancer is the subject of this report.

1) Aspiration Biopsy Cytology

Since Martin and Ellis proposed aspiration biopsy cytology as a breast cancer diagnosis method in 1930[14]. There have been many reports on it. Zajdela et al[23], and Franzén and Zajicek[7] have reported detection rates using it of 91.3% and 89.2%, respectively. The detection rate of aspiration biopsy cytology at our clinic is 91.5% (efficiency 93.0%), reaching 95.7% (90/94) if re-examinations are included. In general, the possible factors affecting diagnosis by aspiration biopsy cytology are : size of tumor, histological types, age of patients, size of breast, judgement of the cytology reader, operator's skill in aspiration biopsy, etc.. The technique of cytology is not discussed in detail in this paper.

Usually, the smaller the size of the tumor and the larger the size of the breast, the more difficult it becomes to identify or fix the location of tumor, thereby leading to difficulty in accurate biopsy (so-called technical error). The detection rate at our clinic for small breast cancers not more than 2.0 cm was 29 of 35 cases (82.9%) and that of not more than 1.0 cm, in particular, was as low as 62.5% (5/8). Kline et al[12] also reported that the rate of technical error due to inadequate biopsy or aspiration was about 50% for the false negative cases and was even higher in small tumors of not more than 0.8 cm. Of the 6 cases of breast cancer not more than 2.0 cm which had been misdiagnosed by aspiration biopsy cytology, 2 cases were clearly considered to fall into the technical error category (insufficient cell materials). In fact, one of the cases was re-diagnosed as cancer by re-aspiration. Of the other 4 cases which had been misdiagnosed as fat necrosis, 2 were re-diagnosed as cancer. We wish to stress the difficulties in diagnosis caused by fat necrosis. This lesion may obscure not only the cytologic slide interpretation but may also obscure the reading of the xeromammography direct malignant positive signs such as microcalcification[16]. The other 2 cases contained many naked bipolar cells and were judged as benign mammary dysplasia (B.M.D.)[15]. Thus, only 3 of the 35 cases (8.6%) were unable to be judged as cancer before open biopsy or operation. The detection rate by histological type was as low as 80% for non-invasive cancer and 85% for scirrhous cancer. The reasons for this may be that non-invasive cancer is generally of a smaller size in many cases[5] and that scirrhous cancer holds sufficient connective tissue that prevents complete aspiration of cells causing an increase in the number of negative cases[12,23]. The detection rate tended to be lower in the younger patients and when the lesions was in the outer half, but these differences were not significant. In contrast, there have been few reports of detailed study on benign disease. Duguid et al[3] reported that it might be difficult to identify fibroadenoma, sclerosing adenosis, duct ectasia, etc.. This difficulty may be because of the coexistence of various histological features in benign disease which allows the needle to aspirate only a part of the complex lesion. In addition, benign diseases do not generally allow easy aspiration of a sufficient amount of cells and it is difficult to judge even their histological type at present. It can be said, however, that if correctly aspirated, there will be very few benign disease cases to misdiagnosed as cancer or so-called false positive. We have misdiagnosed 3 of 72 cases (2 fibrocystic disease and one sclerosing adenosis) as cancer, which were our mistakes that would have been able to be prevented by careful microscopic examinations.

2) Xeromammography

Since the introduction of the "XEROX 125 SYSTEM" of Xerox Co. in 1970, its simple operation procedure has helped xeromammography be gradually popularized in public[6,16,19]. Our clinic introduced the "XEROX 125 SYSTEM" in June 1976. It has been used for diagnosing mammary disease through direct malignant signs and for establishing the high risk group (P2 + DY) with the parenchymal pattern proposed by J.N. Wolfe[19]. The system provides many advantages over the conventional one, such as wider tolerance, more intensified contrast by its edge effect characteristics, wider examinable region, etc.. It is said that its detection rate for breast cancer is about 80—90% through tumor shadow and about 40% through microcalcification[22]. The accuracy in detecting breast cancer obtained at our clinic mainly through these two direct malignant signs was 81.9%. The detection rate was 68.1% and 37.2% by tumor shadow and microcalcification, respectively. The detection rate classified by tumor size was as low as 76.9% for tumors not more than 1.0 cm and showed a true correlation with the tumor size. The detection rate of tumors not more than 2.0 cm through microcalcification was 31.4% including false negative cases by the aspiration biopsy cytology. In many cases, especially of breast cancer up to 1.0 cm, xeromammography is of help for accurate diagnosis[20]. Histologically, the rate was low for solid-tubular and scirrhous cancers. Although there is no definite evidence for this, Feig et al[5] reported that small tumors generally fell into the category of histological grade I and showed a higher positive rate for those of higher grade. Age and location of tumor do not seem to be factors related to misdiagnosis by xeromammography.

In benign cases, microcalcification is known to

sometimes lead to misdiagnosis as cancer[10]. Also at our clinic, microcalcification was observed in 16.7% of mastopathy and 16% of fibroadenoma. Although the rate of false positives is as high as 14.3%, the application of xeromammography is considered to be of great significance as it is capable of detecting small tumors accompanied by microcalcification which are difficult to detect by aspiration biopsy cytology[6].

The detection of breast cancer by the concurrent use of aspiration biopsy cytology and xeromammography is as high as 96.8% (91/94) with a rate of 91.4% even for those tumors 2.0 cm or less. We consider it effective to use both methods which compensates for each of their disadvantages. On the other hand, at present, both methods show low detection rates for small breast cancers and scirrhous cancers not more than 1.0 cm, for which further improvements are needed. For this purpose, it will be necessary to establish a high risk group (P2 + DY) by parenchymal pattern and follow them up carefully[6,19] and to popularize the self-examination[1,2,17,18]. In the case of insufficient aspiration in aspiration biopsy cytology, it could lead to a danger of diagnosing it simply as no malignancy[23]. Thus, it is recommended to re-examine such cases without hesitation. Especially, it is considered unavoidable at present that a small tumor not more than 1.0 cm should be subjected to open biopsy when malignancy is suspected during inspection and palpation even if its aspiration biopsy cytology and xeromammography are negative.

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