Presurgical Determination of Estrogen Receptor Status Using Immunocytochemically Stained Fine Needle Aspirate Smears in Patients with Breast Cancer

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ABSTRACT

We have developed an immunocytochemical staining procedure (ERICA) using a monoclonal antibody to the estrogen receptor (ER) to determine ER status from samples obtained by fine needle aspiration of primary and recurrent breast cancer tissue (cyto-ERICA). ER status was assessable on 214 of 246 smeared aspirates from breast cancer patients. In 143 (66.8%) assessable smears positive nuclear staining was observed but was completely absent in 71 (33.2%) cases. In 107 cases we were able to compare results with those obtained with the quantifiable dextran-coated charcoal (DCC) radioimmunoassay technique using surgically excised material.

We observed qualitative agreement in 53 of 62 (85.5%) of primary specimens and 16 of 16% (100%) recurrent samples compared to the subsequent DCC result on the same sample. Aspirates obtained from new secondary deposits were also assessed and in 16 of 19 (84.2%) cases results agreed with that established previously by DCC on the primary breast tumor. In a further 6 of 10 (60%) cases the cyto-ERICA result obtained from recurrent samples qualitatively agreed with that determined by DCC on a previous recurrent lesion.

A comparison of staining of aspirates was also made against frozen tissue sections stained with the monoclonal antibody (tissue-ERICA). Where comparison was made of primary tumor specimens agreement was observed in 40 of 45 (88.9%) of cases while specimens from secondary lesions agreed qualitatively in 14 of 17 (82.3%) of cases. In a small number of samples where tissue-ERICA was performed on an earlier lesion to that aspirated for cyto-ERICA an agreement of 4 of 5 (80%) was observed.

This technique shows good sensitivity in demonstrating ER in aspirate specimens, should therefore permit us to determine ER status before surgery for primary breast cancer, and may also mean that surgery for recurrent disease to determine receptor status is no longer necessary.

INTRODUCTION

The determination of ER2 status of breast cancer is a recognized prerequisite in selecting systemic endocrine therapy in breast cancer (1). This has led to the raising of a number of monoclonal antibodies to the human ER and subsequently to the development of an immunocytochemical assay for visualizing this protein in tissue sections (2-4). This technique (ERICA) offers certain advantages over the radioimmunoassay technique (cyto-ERICA) which may reduce the need for biopsies of tumor samples.

RESULTS

Smear preparations were obtained for standard cytological examination (9) and for cyto-ERICA analysis from 217 patients with suspected or proved cancer of the breast. Two hundred forty-six sites were aspirated, 25 patients having more than 1 site investigated. One hundred twenty-one aspirates from 217 patients presenting with breast lumps to clinics at the Royal Marsden Hospital (Surrey Branch) and St. George's Hospital, Tooting, were taken and were found to be cytologically suspicious or definitely malignant. Clinical tumor (T)-nodes (N)-metastasis (M) staging was performed on 82 patients at presentation. One patient had a T0 stage tumor, 6 patients had T1 stage tumors, 44 had T2 stage tumors, 13 had T3 stage tumors, and 18 had T4 stage tumors. Fifty-five patients had no clinical nodal involvement (N0), 24 were stage N1, and 3 were stage N2 clinically. Full details were not recorded on 25 patients. One hundred four aspirates were also taken from patients with histologically confirmed locally advanced or metastatic breast cancer. Forty-eight of these metastatic aspirates were obtained from local breast mass recurrences, 25 from lymph nodes, and 31 from distant skin lesions. A further 21 aspirated from supposed recurrent tissues showed only benign cells present.

The DCC assay was performed on biopsies from 62 primaries and 16 recurrences. Tissue-ERICA was performed on 45 primaries and 17 recurrences. DCC-ER status had previously been established on 19 and tissue-ERICA status was done on 5 further primary specimens where aspiration for cyto-ERICA was performed on a recurrent nodule or lump. Similarly 10 earlier recurrent lesions had been analyzed by DCC where cyto-ERICA analysis was undertaken on a later recurrence of disease. No such comparison has been made with tissue-ERICA specimens.

Immunocytochemical ERICA Procedure for Fine Needle Aspiration (Cyto-ERICA)

Specimen Preparation. Breast lumps or skin nodules were aspirated in a similar way to that used for obtaining smears for normal cytological investigation using a 21-gauge hypodermic needle. Smears were immediately made on poly-l-lysine-coated glass slides (coated using ERICA kit reagents) and rapidly frozen in dry ice (−78 °C). Specimens were transported to the laboratory frozen and stored at −78°C for up to 10 days before staining. Two to 4 slides were prepared from each sample for cyto-ERICA analysis and a further 2 smears from the same aspirate were air dried and sent for routine cytological examination (9).

Rapid freezing of specimens immediately after smearing ensured that use of polyethylene glycol or similar compounds to decrease receptor lability was unnecessary. However, time course studies showed that excess delay in freezing smears or allowing them to air dry frequently caused some receptor staining loss. This was therefore avoided, since it may cause false negative results in specimens with initially low levels

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1 To whom requests for reprints should be addressed.

2 The abbreviations used are: ER, estrogen receptor; ERICA, estrogen receptor immunocytochemical assay; DCC, dextran-coated charcoal; PBS, phosphate-buffered saline; cyto-ERICA, ERICA from fine needle aspirates; tissue-ERICA, ERICA from frozen tissue sections stained with the monoclonal antibody.

6118
of ER and make semiquantitation of results invalid. With ER-rich specimens little effect was noted.

**Fixation.** Frozen slides were immersed in 3.6% formal-PBS (pH 7.2) at room temperature for 10 min. They were then washed twice in PBS for a total of 10 min and immersed in absolute methanol (−20°C) for 4 min followed by acetone (−20°C) for 1–2 min. Slides were then washed again twice in PBS (room temperature) for 10 min.

No appreciable reduction in ER staining occurred if slides were then stored in a cold (−20°C) glycerol/sucrose preparation (10) for up to 4 weeks preceding staining.

**Staining Procedure.** We utilized the H222 monoclonal antibody ERICA kit (Abbott Laboratories, Chicago, IL). The staining procedure has been well documented previously for H226 (4) and H222 antisera (6, 7). Following an indirect peroxidase-antiperoxidase procedure similar to that of Sternberger et al. (11), visualization of receptor was achieved through the diaminobenzidine hydrochloride:hydrogen peroxide chromogen-substrate reaction. Counterstaining was in 1% (v/v) Harris hematoxylin in distilled water for 5 min. Slides were then dehydrated and mounted in a xylene-soluble mountant. Interpretation of slides was performed without knowledge of the DCC results by one of us (U. B.).

**Validity of Smear Material.** Smear preparations were accepted for staining assessment only if they satisfied certain criteria: (a) routinely prepared, Giemsa-stained cytological preparations showed tumor cells present; (b) cyto-ERICA smear contained cells with easily identifiable epithelial cell characteristics.

ERICA-stained epithelial cells were distinguishable from nonepithelial cells in smears, but it was not always possible to distinguish normal or benign cells from carcinoma cells, and consequently confirmation of tumor cell presence was obtained from the Giemsa-stained slides.

**Tissue-ERICA**

**Specimen Preparation and Staining Procedure.** Biopsy specimens from primary or recurrent lesions were trimmed of excess fat and connective tissue, snap frozen in liquid nitrogen within 15 min of excision, and transported to the laboratory on dry ice. Specimens were divided in two while frozen and one portion was sent for DCC ER analysis; the remainder was cut for tissue-ERICA.

Tissue fixation and staining procedures for tissue-ERICA are described in detail elsewhere (6, 7) (also see above).

**Dextran-coated Charcoal Technique**

This procedure has been described in full detail elsewhere (12, 13), with the few modifications outlined by McClelland et al. (6).

**Statistical Methods**

Tissue-ERICA, cyto-ERICA, and DCC results were regarded as qualitative measurements of ER positivity, each dividing the patient population into ER-positive and ER-negative groups. The significance of the association between the different ER measurements was assessed using the Mantel-Haenzel test (14). Since the study aimed to establish the validity of fine needle aspirate ER assessment, cyto-ERICA results were compared against the DCC and tissue-ERICA techniques which were taken as standard. The sensitivity and specificity of the procedure were calculated on this basis.

The quantitative associations between cyto-ERICA, DCC, and tissue-ERICA were assessed using Spearman rank correlation tests.

**RESULTS**

Specific immunostaining was observed in the nuclei of tumor cells in 143 of 214 (66.8%) of assessable cases (Table 1; Fig. 1). The percentage of tumor cells stained in the smears varied between <1 and 100%. In 32 cases no assessable material was obtained in the aspirate, or Giemsa-stained smears showed no evidence of benign or tumor cells present. Of the unassessable cases 8 were from primary breast cancer: 3 were stage T2 clinically; 2 were T3; and 3 were unknown. A further 17 unassessable aspirates were from recurrent breast cancer and 7 were from benign disease.

For the purpose of this study the presence of any number of positively stained tumor cells in both aspirates and sections was taken to be positive. This contrasts with our established cutoff for positivity (5, 6) where tissue-ERICA cutoff used was ≥50% tumor cells stained. In this study such a cutoff was considered unnecessary since we wished to directly compare the two ERICA techniques and on occasions small cell numbers found in some aspirates made such a cutoff invalid. An evaluation of a threshold level for cyto-ERICA positivity for the purposes of

<table>
<thead>
<tr>
<th>Primary breast cancer</th>
<th>80 (70.8)*</th>
<th>33 (29.2)</th>
<th>8</th>
<th>121</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent breast cancer</td>
<td>57 (65.5)</td>
<td>30 (34.5)</td>
<td>17</td>
<td>104</td>
</tr>
<tr>
<td>Benign breast disease</td>
<td>6 (42.9)</td>
<td>8 (57.1)</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>143 (66.8)</td>
<td>71 (33.2)</td>
<td>32</td>
<td>246</td>
</tr>
</tbody>
</table>

* Cyto-ERICA positivity, presence of any number of specifically stained tumor cell nuclei. Distribution of ER in primary breast cancers, recurrent breast cancers, and benign breast diseases as determined using the cyto-ERICA technique on fine needle aspirates obtained from these tissues. The cyto-ERICA status of some samples was not assessable due to lack of relevant material being present in the stained smear, particularly seen with aspirates from benign breast lesions.

Numbers in parentheses, percentage.
ESTROGEN RECEPTORS IN BREAST ASPIRATES

Table 2  Estrogen receptor status as determined by cyto-ERICA and DCC procedures

<table>
<thead>
<tr>
<th></th>
<th>A. Cyto-ERICA positive, DCC positive</th>
<th>B. Cyto-ERICA positive, DCC negative</th>
<th>C. Cyto-ERICA negative, DCC positive</th>
<th>D. Cyto-ERICA negative, DCC negative</th>
<th>Total</th>
<th>Overall agreement (A + B + C + D) - (B + C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyto-ERICA and DCC assessed on primary specimens</td>
<td>44 (71)*</td>
<td>6 (9.7)</td>
<td>3 (4.8)</td>
<td>9 (14.5)</td>
<td>62</td>
<td>53</td>
</tr>
<tr>
<td>Cyto-ERICA and DCC assessed on same recurrent specimens</td>
<td>12 (75)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>4 (25)</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>DCC assessed on primary cyto-ERICA assessed on recurrence</td>
<td>14 (73.7)</td>
<td>1 (5.3)</td>
<td>2 (10.5)</td>
<td>2 (10.5)</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>DCC assessed on earlier recurrence than cyto-ERICA</td>
<td>2 (20)</td>
<td>3 (30)</td>
<td>1 (10)</td>
<td>4 (40)</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>72 (67.3)</td>
<td>10 (9.3)</td>
<td>6 (5.6)</td>
<td>19 (17.8)</td>
<td>107</td>
<td>91</td>
</tr>
</tbody>
</table>

* Cyto-ERICA positivity, presence of any number of specifically stained tumor cell nuclei. DCC positivity, >15 fmol/mg cytosol protein. The comparability of the cyto-ERICA technique with the well established DCC procedure is examined in Table 2. Cyto-ERICA was assessed on a fine needle aspirate smear and compared with ER status determined on surgically excised tissue obtained as indicated. Note: DCC cutoff previously established as optimum for prediction of outcome of endocrine therapy (6). * Numbers in parentheses, percentage.

Table 3 Cyto-ERICA test for estrogen receptor: comparability with standard procedure (DCC)

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Overall agreement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyto-ERICA and DCC assessed on primary specimens</td>
<td>22.0</td>
<td>94</td>
<td>60</td>
<td>85.5</td>
</tr>
<tr>
<td>Cyto-ERICA and DCC assessed on same recurrent specimens</td>
<td>14.0</td>
<td>88</td>
<td>67</td>
<td>84.2</td>
</tr>
<tr>
<td>DCC assessed on primary cyto-ERICA assessed on recurrence</td>
<td>2.7</td>
<td>67</td>
<td>57</td>
<td>60</td>
</tr>
<tr>
<td>DCC assessed on earlier recurrence than cyto-ERICA</td>
<td>Total (n = (95))</td>
<td>22.8</td>
<td>92</td>
<td>66</td>
</tr>
</tbody>
</table>

* The Mantel-Haenzel homogeneity test ($x^2 = 5.94, d.f. = 3$) shows no significant difference in odds ratio between groups. * Not all specimens recorded in Table 2 are evaluated since in some cases small sample size made such assessment inappropriate.

Table 4 Estrogen receptor status as determined by cyto-ERICA and tissue-ERICA procedures

<table>
<thead>
<tr>
<th></th>
<th>A. Cyto-ERICA positive, tissue-ERICA positive</th>
<th>B. Cyto-ERICA positive, tissue-ERICA negative</th>
<th>C. Cyto-ERICA negative, tissue-ERICA positive</th>
<th>D. Cyto-ERICA negative, tissue-ERICA negative</th>
<th>Total</th>
<th>Overall agreement (A + B + C + D) - (B + C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyto-ERICA and tissue-ERICA assessed on primary specimens</td>
<td>32 (71.1)*</td>
<td>4 (8.9)</td>
<td>1 (2.3)</td>
<td>8 (17.8)</td>
<td>45</td>
<td>40</td>
</tr>
<tr>
<td>Cyto-ERICA and tissue-ERICA assessed on same recurrent specimens</td>
<td>10 (58.8)</td>
<td>2 (11.8)</td>
<td>1 (5.9)</td>
<td>4 (23.5)</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Tissue-ERICA assessed on earlier specimen than cyto-ERICA</td>
<td>4 (80)</td>
<td>0</td>
<td>1 (20)</td>
<td>0</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>46 (68.7)</td>
<td>6 (8.9)</td>
<td>3 (4.5)</td>
<td>12 (17.9)</td>
<td>67</td>
<td>58</td>
</tr>
</tbody>
</table>

* Cyto-ERICA and tissue-ERICA positivity, presence of any number of specifically stained tumor cell nuclei. The comparability of the cyto-ERICA and tissue-ERICA techniques is examined in Table 4. Cyto-ERICA was assessed on a fine needle aspirate smear and compared with ER status determined on fixed frozen sections of surgically excised material by tissue-ERICA. * Numbers in parentheses, percentage.

Table 5 Cyto-ERICA test for estrogen receptor: comparability with standard procedure (tissue-ERICA)

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Overall agreement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyto-ERICA and tissue-ERICA assessed on primary specimens</td>
<td>64.0</td>
<td>97</td>
<td>67</td>
<td>89</td>
</tr>
<tr>
<td>Cyto-ERICA and tissue-ERICA assessed on same recurrent specimens</td>
<td>20.0</td>
<td>91</td>
<td>67</td>
<td>82</td>
</tr>
<tr>
<td>Tissue-ERICA assessed on earlier recurrence than cyto-ERICA</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Total (n = (59))</td>
<td>61.3</td>
<td>94</td>
<td>67</td>
<td>82</td>
</tr>
</tbody>
</table>

* Not all specimens recorded in Table 4 are evaluated since in some cases small sample size made such assessment inappropriate.

Accurate prediction of endocrine therapy response is currently being undertaken. DCC positivity was taken to be ≥15 fmol/mg cytosol protein.

Breast Carcinoma. Specific staining by cyto-ERICA agreed qualitatively with the DCC assay in 69 of 78 (88.5%) breast tumor specimens where both assays were performed on material from the same lesion (Tables 2 and 3) and in a further 22 of 29 (75.9%) samples where tissue for DCC was obtained prior to that for cyto-ERICA. Specific staining by cyto-ERICA agreed with staining results of tissue-ERICA on sections in 54 of 62 (87.1%) cases where tissue and aspirate were obtained from the same lesion (Tables 4 and 5). In 4 of 5 (80%) cases agreement...
was observed where tissue was obtained from an earlier lesion than that aspirated for cyto-ERICA.

Eighth of 113 (70.8%) assessable primary breast cancer aspirates were found to contain specific receptor-positive cells. On 62 of these cancers both cyto-ERICA and DCC were performed and agreement between receptor status was observed in 53 (85.5%). Of the 9 which did not agree 3 were negative by cyto-ERICA but were found to be positive by the DCC method and 6 cases were negative by DCC but showed staining of a number of cells by cyto-ERICA. Tissue-ERICA comparison was made on 45 specimens (Tables 4 and 5). Status agreement was observed in 40 of 45 (88.9%) of cases. Of the 5 which did not show agreement, 4 were cyto-ERICA positive and tissue-ERICA negative.

Fifty-seven of 87 (65.5%) assessable recurrent lesions examined were positive by cyto-ERICA. Where direct comparison between DCC and cyto-ERICA results was possible, agreement was observed in 16 of 16 cases. Status correlation was seen in 16 of 19 (84.2%) cases in which DCC was performed on the primary lesion and cyto-ERICA on a recurrent lesion and in 6 of 10 (60%) of cases in which DCC tissue was obtained from an earlier recurrence than that aspirated for cyto-ERICA (Tables 2 and 3). Tissue-ERICA was performed on 17 recurrent specimens from which cyto-ERICA aspirates had been obtained and agreement was found in 14 (82.3%) of cases. A further 5 specimens were compared where tissue was obtained from an earlier lesion than that aspirated for cyto-ERICA and agreement here was 4 of 5 (80%) (Tables 4 and 5).

Overall cyto-ERICA results agreed with DCC results in 91 of 107 (85.0%) cases (82 positive by cyto-ERICA, 78 positive by DCC) and with tissue-ERICA in 58 of 67 (86.6%) of cases (52 positive by cyto-ERICA, 49 positive by tissue-ERICA).

Assuming DCC and tissue-ERICA estimations of ER to be correct, cyto-ERICA showed good sensitivity when compared with these, selecting 92% of DCC positives and 94% of tissue-ERICA positives as cyto-ERICA positive (Tables 3 and 5). However, the specificity of the technique was somewhat lower, 66% against DCC and 67% against tissue-ERICA.

Odds ratios between the tests (Tables 3 and 5) did not differ significantly between the separate groups illustrated (e.g., Mantel-Haenzel homogeneity test, $x^2 = 5.94$, d.f. = 3 for DCC versus cyto-ERICA). The test may therefore be assumed to have similar validity for these different groups.

Scatter plots of the data described in Tables 2 to 5 are presented (Figs. 2 and 3). Spearman rank correlation coefficients for DCC versus cyto-ERICA ($Ps = 0.48$) and for tissue-ERICA versus cyto-ERICA ($Ps = 0.41$) were observed.

Benign Breast Disease. Specific staining was observed in 6 of 14 assessable benign breast aspirates. A study investigating ER in aspirates from both benign disease and normal breast is currently ongoing in our laboratory.

**DISCUSSION**

The use of a cytological technique for ER assessment offers certain potential advantages in the management of breast cancer over the conventionally used biochemical method. It requires very small amounts of tissue for assessment, allowing determinations to be made on small recurrent lesions. Furthermore needle aspirates spare patients unnecessary surgery when such is performed for ER determination.

This report shows good overall agreement between ER status determined by such a cytological ER immunochromeprocedure, a conventional DCC assay, and an immunocytochemical procedure for use on frozen sections. It demonstrates overall agreement between cytological and DCC ER status determination in 85% of cases. Agreement is shown between the two immunochromeprocedures in 87% of cases.

The technique demonstrates good sensitivity with few false
negatives being observed when assessed against DCC and tissue-ERICA which are taken as standards for the validation of this technique. The specificity of the technique, however, is poor, since cyto-ERICA classifies a number of specimens positive which are classified negative by the other procedures. This in part may be attributable to assay positivity threshold level variations between DCC and cyto-ERICA, since DCC positivity is assumed at ≥15 fmol/mg cytosol protein and cyto-ERICA smears were classified positive if any number of tumor cell nuclei were observed to be positively stained.

Intrasutural variations in ER content have been observed using DCC analyses on distinct sections of large tumors (15), and heterogeneity in ER expression using ERICA on sections has also been reported (8). It seems probable therefore that poor cytological samples may occasionally be subject to misinterpretation if unrepresentative areas of a lesion are aspirated.

In 6 of 107 cases cyto-ERICA negative smears were obtained from tumors which contained significant levels of ER by DCC analyses. In 10 cases aspirates were found to contain immunoreactive cells but to below the threshold level of positivity for the DCC assay and this demonstrates the need for further study into the possible semiquantitation of this technique. Similar nonagreements between cyto-ERICA and tissue-ERICA may also be due to intrasutural sampling variations.

Aspiration of occasional normal breast ductal epithelial cells which are frequently ERICA positive may account in part for the few contrasting cyto-ERICA-positive, tissue-ERICA-negative results observed. However, this explanation presupposes a lack of such normal cells in the routine Giemsa-stained preparation since examination of this would allow their exclusion. False negative results with cyto-ERICA may also result from poor sample handling, in particular delay in freezing freshly made smears. However, in 4 of these cases in which DCC, cyto-ERICA, and tissue-ERICA were all performed, cyto-ERICA did correlate with one procedure result. Appreciable loss of receptor is sometimes observed if smears are allowed to air dry before freezing. The monitoring of such preparation in clinics would therefore be necessary by a trained cytopathologist when introducing this procedure and inadequate samples should be repeated since the procedure is relatively pain free.

Possible pitfalls in interpretation include nonspecific cytoplasmic reactions due to endogenous peroxidase expression by some leukocytes, histiocytes, and in particular erythrocytes. In addition areas of fat tissue are also occasionally weakly stained. However, the inclusion of a second control smear from every patient stained with a normal rat IgG antibody enables fairly simple interpretations and exclusion of these nonspecifically stained cells.

Future studies will be directed at quantifying aspirate staining to enable a more accurate threshold level of positivity to be established. We have investigated this in relation to cyto-ERICA staining as a means of predicting outcome to endocrine therapy but at present, in a small number of patients, the presence of any number of positive cells appears to be the most accurate predictor. The future role of fluorescence-activated cell sorting for quantitation of ER content of aspirate is also currently being investigated.

ACKNOWLEDGMENTS

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