Hormone Receptor and c-ERBB2 Status in Distant Metastatic and Locally Recurrent Breast Cancer

Pathologic Correlations and Clinical Significance

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Key Words: Breast cancer; Discordance; Hormone receptors; c-ERBB2; Metastases; Local recurrence

DOI: 10.1309/AJCPJ57FLLJRXXPV

Abstract

Estrogen receptor (ER), progesterone receptor (PR), and c-ERBB2 (HER2/neu) are therapeutically and prognostically important markers in the management of breast carcinoma. They are not always analyzed in distant metastatic and locally recurrent breast cancers. We compared immunohistochemical expression in a series of primary breast carcinomas with their distant metastases (n = 72) and local recurrences (n = 45) and analyzed the impact of any changes on survival. Discordance rates between primary and metastatic and between primary and locally recurrent lesions, respectively, were 18% (13/72) and 13% (6/45) for ER, 42% (30/72) and 33% (15/45) for PR, and 7% (5/72) and 2% (1/45) for c-ERBB2. There was statistically significant discordance between primary and metastatic PR status (P = .017; \( \kappa = 0.201 \)). Among locally recurrent tumors, 15 (33%) of 45 revealed discordance for PR (P = .006; \( \kappa = 0.366 \)). We observed a trend for shorter survival among women with \( \text{ER}^- \) metastatic and locally recurrent tumors regardless of the primary tumor ER status. Our findings suggest a benefit for routine evaluation of ER, PR, and c-ERBB2 status in distant metastatic and locally recurrent breast cancer for therapeutic and prognostic purposes.

Estrogen receptor (ER), progesterone receptor (PR), and c-ERBB2 (HER2/neu) are therapeutically and prognostically important markers in the management of breast carcinoma. About 60% to 70% of breast carcinomas express ER protein, and these tumors are associated with better prognosis. Detecting ER expression in a tumor depends on physiologic and technical factors, including menopausal status, endocrine therapy, tumor sampling and intratumoral heterogeneity, tissue fixation, method of examination (biochemical, immunohistochemical), and type of antibody used.

ER status is important in predicting the response to adjuvant tamoxifen (hormonal) therapy. Desombre and Jensen demonstrated a decrease in the ER content as a tumor progresses. PR is a surrogate marker of functional ER because PR is an estrogen-regulated gene. More than half of ER+ tumors express PR. Hence, simultaneous analysis of ER and PR gives more information regarding likely hormonal response. Some studies have reported the presence of PR as a better predictive marker of response to hormone therapy than quantitative ER. Of breast carcinomas, 55% express both ER and PR, whereas 22% do not express either ER or PR. In addition, 20% of tumors are ER+ and PR−, and 3% are ER− and PR+. Humanized epidermal growth factor receptor 2 (c-ERBB2) is a proto-oncogene, located on chromosome 17, encoding a 185-kDa transmembrane tyrosine kinase receptor for an unknown growth factor. The c-ERBB2 oncogene is altered by gene amplification, causing protein overexpression in a wide variety of human epithelial malignancies. Such alterations activate signaling systems that promote cell growth, angiogenesis, and cancer metastases.
oncogene c-ERBB2 is amplified and/or overexpressed in approximately 25% of breast cancers and is associated with aggressive disease as shown by an association with shorter disease-free survival (DFS) and overall survival (OS) of women, although more recent studies have indicated a lower rate of c-ERBB2 overexpression, about 18%. Carcinomas that overexpress c-ERBB2 respond to treatment with humanized anti-c-ERBB2 monoclonal antibody (trastuzumab) and are associated with resistance to hormonal therapy. Binding of trastuzumab to c-ERBB2 blocks growth stimulating intracellular signaling and decreases the cellular repair capacity after chemotherapy, possibly also improving apoptosis.

Administration of trastuzumab with chemotherapeutic agents has been shown to produce longer DFS and OS, with 25% to 50% of c-ERBB2+ patients with metastatic breast cancer responding favorably to trastuzumab. Treatment failure could be a result of heterogeneity in expression of c-ERBB2 in the primary tumor and its metastases.

Several studies have investigated expression of hormonal receptors of primary breast carcinomas and their metastases, mainly comparing ER and PR status of the primary tumor with regional nodal metastases. Some authors have lumped local recurrences and distant metastases together as 1 group. Distant metastases, however, may not be biologically equivalent to local recurrences or regional axillary lymph node metastases, potentially behaving as clonal outgrowths with genetic modifications that may not be detectable in the primary tumors. Data referring to distant metastases are scant, with studies comparing primary and distant metastases using small numbers of patients. Studies specifically relating receptor status of primary tumors with local recurrences are also few.

Mobbs et al demonstrated 19% discordance of ER and 33% discordance of PR between primary and secondary tumors with no intervening treatment. With intervening chemotherapy and/or irradiation, overall discordance in hormone receptor status was 24%. Hormone receptor status between primary and secondary tumors may be altered whether the secondary tumor is locally recurrent or metastatic. Studies using immunohistochemistry, fluorescence in situ hybridization (FISH), or both have reported a high level of consistency, although not absolute, in c-ERBB2 status in primary tumors, locoregional recurrences, and distant metastases. Santinelli et al reported 13.3% discordance of c-ERBB2 in local recurrences compared with the primary tumor.

In this study, we compared ER, PR, and c-ERBB2 status in series of primary breast carcinomas with their local recurrences and distant metastases. In addition, we analyzed the impact of changes of hormonal and c-ERBB2 status on survival.

Materials and Methods

Files of the Department of Pathology, Singapore General Hospital, Singapore, were searched for cases of primary breast carcinoma with subsequent histologically proven local recurrences and distant metastases during the period from 1991 to 2007. The study cohort included 72 distant metastatic and 45 locally recurrent lesions. Local recurrence was defined as tumor recurring in the ipsilateral breast in patients who had undergone wide excision or on the chest wall in patients who underwent mastectomy. Distant metastasis referred to metastatic tumor at distant sites, away from locoregional locations, and excluded axillary nodal metastases.

Clinicopathologic Features

Data on primary breast cancers, local recurrences, and distant metastases were obtained from accession forms. Age, ethnicity, date of initial primary invasive breast cancer diagnosis, date of locally recurrent or distant metastatic cancer diagnosis, and location of distant metastases were documented. Patient follow-up was derived from case notes.

Given the relatively long period during which the present patient series was derived, standards of therapy differed during several periods. Before 1998, adjuvant tamoxifen was restricted to postmenopausal women with hormone receptor–positive early breast cancer. Information published in 1998 led to a shift in treatment paradigm, and all women with hormone receptor–positive early breast cancer were offered adjuvant tamoxifen regardless of menopausal status. Third-generation aromatase inhibitors (anastrozole, letrozole, and exemestane) were offered to postmenopausal women with hormone receptor–positive early breast cancer after 2004. Women with primary tumor size larger than 2 cm and/or any axillary lymph node involvement were counseled for adjuvant chemotherapy. Regimens mostly comprised classical cyclophosphamide, methotrexate, and 5-fluorouracil and doxorubicin-cyclophosphamide. After 2003, doxorubicin-cyclophosphamide followed by paclitaxel became the institutional standard of care for patients with lymph node–positive early breast cancer. Radiation treatment was administered to all conservatively resected breast cancers and to patients with 4 or more involved axillary nodes and primary tumors larger than 5 cm. After 2006, adjuvant trastuzumab (Herceptin) was offered to patients with c-ERBB2+ primary breast cancer that was larger than 1 cm or that involved any axillary lymph nodes.

Immunohistochemical Analysis

For immunohistochemical analysis, 4-μm sections from primary tumors and their histologically proven metastases or recurrences were stained with anti-ER, anti-PR, and anti-c-ERBB2 using routine protocols, performed at the same
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time under identical conditions. Briefly, paraffin sections of the formalin-fixed tissue were stained for ER (SP1, catalog No. RM9101-S, dilution 1:50; NeoMarkers, Fremont, CA), PR (PgR636, catalog No. RM9102-S, dilution 1:200; NeoMarkers), and cERBB2 (SP3, catalog No. RM9103-S, dilution 1:200; NeoMarkers). The sections were pretreated using a microwave at 98°C for 12 minutes in Ventana CCI solution (Ventana Medical Systems, Tucson, AZ). The detection system used was LSAB (linked streptavidin biotin, DAKO, Glostrup, Denmark).

Immunohistochemical staining was defined as nil (no staining), 1+ (mild), 2+ (moderate), and 3+ (strong) staining. For ER and PR, a result was considered positive if at least 10% of tumor cells displayed a minimal 2+ nuclear staining. It is recognized that this threshold of positivity exceeds that described in other schemes such as the Allred system.27 However, we have used this cutoff that we had previously benchmarked against the H score.1 For c-ERBB2, a test was considered positive if at least 30% of tumor cells exhibited 3+ cell membrane staining, and a borderline/equivocal result was given when at least 10% of lesional cells showed 2+ cytoplasmic membrane staining. Results that failed to fulfill the aforementioned criteria were considered negative. We did not use FISH for c-ERBB2 in this study because our laboratory protocol is to apply FISH for an equivocal result, which was not encountered in the cases.

Statistical Analysis

Findings were analyzed by using statistical software SPSS for Windows, version 11.5 (SPSS, Chicago, IL). Association of hormone receptor status and c-ERBB2 expression between primary and metastatic and between primary and recurrent lesions was analyzed by using the $\chi^2$ test. A $P$ value of less than .05 defined statistical significance. In addition, we used $\kappa$ values to analyze the agreement of results between primary and metastatic and between primary and locally recurrent lesions. The $\kappa$ statistic measured agreement between 2 sets of categorical data. Values of $\kappa$ from 0 to 0.2 were regarded as no agreement, 0.21 to 0.4 as fair agreement, 0.41 to 0.6 as moderate agreement, 0.61 to 0.8 as substantial agreement, and 0.81 to 1 as almost perfect agreement.

OS was calculated as the period from the date of initial primary diagnosis to the date of death. DFS was defined as the length of time before the appearance of a metastatic or locally recurrent lesion. Survival time was calculated from the time of first documented metastasis or recurrence to death or last follow-up. Survival curves were established using the Kaplan-Meier method. The log-rank test was used to compare the survival of patients in the 4 combinations of results of ER and PR in primary and metastatic tumors. To improve the strength of survival analysis, metastatic and locally recurrent tumors were grouped together.

Results

Table 1 and Table 2 summarize the characteristics of the primary tumors. Treatment modalities of the 117 primary tumors consisted of wide excision in 6 cases (5.1%), wide excision with axillary clearance in 15 (12.8%), simple mastectomy with axillary clearance in 94 (80.3%), with 1 case (0.9%) each of mastectomy and radical mastectomy with axillary clearance. The sites of distant metastases were bone (35/72 [49%]), skin (10/72 [14%]), brain (6/72 [8%]), lung (5/72 [7%]), pleura (5/72 [7%]), omentum (3/72 [4%]), pericardium (3/72 [4%]), ovary (2/72 [3%]), intestine (1/72 [1%]), adrenal gland (1/72 [1%]), and liver (1/72 [1%]).

Discordance rates between primary and metastatic and between primary and locally recurrent lesions, respectively, were 18% (13/72) and 13% (6/45) for ER, 42% (30/72)
and 33% (15/45) for PR, and 7% (5/72) and 2% (1/45) for c-ERBB2. Table 3 and Table 4 summarize the concordance and discordance rates between primary and metastatic tumors and between primary and locally recurrent tumors for ER, PR, and c-ERBB2 results. There was a statistically significant level of discordance between primary and metastatic tumors in PR status (30/72 [42%]; \(P = .017; \kappa = 0.201\)). Among locally recurrent tumors, 15 (33%) of 45 revealed discordance for PR (\(P = .006; \kappa = 0.366\)), which was also statistically significant.

If the Allred scheme had been used to assess ER and PR status, there would be 6 cases considered negative in our method that would be regarded as positive (4 primary cancers, 1 local recurrence, and 1 distant metastasis). For PR, there would be 18 cases (7 primary cancers, 7 local recurrences, and 4 distant metastases) similarly concluded. In terms of agreement between ER and PR staining results of primary tumors vs distant metastatic lesions, the Allred scheme would achieve \(\kappa\) values of 0.584 and 0.280, respectively, representing a lower level of agreement for ER compared with our method and a similar band of concordance for PR. For primary tumors vs local recurrences, the Allred scheme would achieve a \(\kappa\) value of 0.815 for ER and 0.689 for PR, representing improved agreement for ER and PR compared with our method.

### Table 3
Comparison of ER, PR, and c-ERBB2 Status in 72 Cases of Primary and Metastatic Tumors

<table>
<thead>
<tr>
<th>Primary/Metastatic Lesion</th>
<th>ER+</th>
<th>ER-</th>
<th>PR+</th>
<th>PR-</th>
<th>c-ERBB2+</th>
<th>c-ERBB2-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrative ductal carcinoma, not otherwise specified</td>
<td>23</td>
<td>19</td>
<td>19</td>
<td>23</td>
<td>8</td>
<td>34</td>
</tr>
<tr>
<td>Infiltrative lobular carcinoma</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Metaplastic carcinoma</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Histologic grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1</td>
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<td>1</td>
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<td>6</td>
<td>7</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>17</td>
<td>13</td>
<td>18</td>
<td>5</td>
<td>26</td>
</tr>
</tbody>
</table>

*ER, estrogen receptor; PR, progesterone receptor; +, positive; –, negative.

### Table 4
Comparison of ER, PR, and c-ERBB2 Status in 45 Primary and Locally Recurrent Tumors

<table>
<thead>
<tr>
<th>Primary/Recurrent Lesion</th>
<th>ER+</th>
<th>ER-</th>
<th>PR+</th>
<th>PR-</th>
<th>c-ERBB2+</th>
<th>c-ERBB2-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrative ductal carcinoma, not otherwise specified</td>
<td>23</td>
<td>16</td>
<td>13</td>
<td>8</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>Infiltrative lobular carcinoma</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Metaplastic carcinoma</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Histologic grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>10</td>
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<td>6</td>
<td>7</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>17</td>
<td>13</td>
<td>18</td>
<td>5</td>
<td>26</td>
</tr>
</tbody>
</table>

*ER, estrogen receptor; PR, progesterone receptor; +, positive; –, negative.

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Table 5 and Table 6 depict adjuvant hormone therapy compared with ER and PR status of the primary breast carcinoma and the recurrences. Among patients who received adjuvant hormonal treatment, 9 (18%) of 49 cases converted from ER positivity in the primary tumor to ER negativity in the recurrences. This compares with 3 (4%) of 68 cases among patients not treated with hormones. For PR, the corresponding numbers were 22 (54%) of 41 and 15 (20%) of 76 cases, respectively. In our series, only 1 patient was treated with adjuvant trastuzumab. Her tumor was 100 mm with axillary lymph node metastases. The primary tumor showed positive results for ER, PR, and c-ERBB2. Metastasis to the T12 vertebra that also demonstrated positivity for ER, PR, and c-ERBB2 occurred after 38.5 months.

Follow-up

In this study, 22 patients died (18.8%), and 95 patients (81.2%) were still alive at the end of follow-up. The OS for patients who died ranged from 15.5 to 130.0 months. The median follow-up time for patients who died was 59.5 months and for patients still alive was 92.3 months. Table 7 summarizes the DFS, OS, and survival times after occurrence of metastases and local recurrences. Figure 1 and Figure 2 show the Kaplan-Meier survival curves from the onset of metastasis and local recurrence for ER and PR status, respectively, in the primary tumors and their metastases and recurrences. Although it is acknowledged that distinction of metastases from local recurrences would be more meaningful, the limited numbers in each category hampered separate

Image 11 Primary breast carcinoma was of the infiltrative ductal (not otherwise specified) subtype (A, H&E, ×200), and pericardial metastases subsequently developed (C, H&E, ×400). Although the primary tumor was negative for estrogen receptor (ER) by immunohistochemical analysis (B, ×400), the pericardial metastasis showed distinct nuclear reactivity for ER (D, ×400).
Primary breast carcinoma of the infiltrative ductal (not otherwise specified) subtype (A, H&E, ×200) with positive progesterone receptor (PR) immunohistochemical staining (B, ×200). There was later occurrence of pleural nodules histologically confirmed as metastasis (C, H&E, ×200) that were negative for PR by immunohistochemical analysis (D, ×400).

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Adjuvant Hormonal Treatment Compared With ER Status of the Primary Breast Carcinoma and Recurrences (Local Recurrences and Distant Metastases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant hormonal treatment</td>
<td>Primary ER–</td>
</tr>
<tr>
<td>Recurrences ER–</td>
<td>0</td>
</tr>
<tr>
<td>Recurrences ER+</td>
<td>0</td>
</tr>
<tr>
<td>No adjuvant hormonal treatment</td>
<td>Recurrences ER–</td>
</tr>
<tr>
<td>Recurrences ER+</td>
<td>7</td>
</tr>
</tbody>
</table>

ER, estrogen receptor; +, positive; −, negative.

<table>
<thead>
<tr>
<th>Table 6</th>
<th>Adjuvant Hormonal Treatment Compared With PR Status of the Primary Breast Carcinoma and Recurrences (Local Recurrences and Distant Metastases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant hormonal treatment</td>
<td>Primary PR–</td>
</tr>
<tr>
<td>Recurrences PR–</td>
<td>0</td>
</tr>
<tr>
<td>Recurrences PR+</td>
<td>0</td>
</tr>
<tr>
<td>No adjuvant hormonal treatment</td>
<td>Recurrences PR–</td>
</tr>
<tr>
<td>Recurrences PR+</td>
<td>8</td>
</tr>
</tbody>
</table>

PR, progesterone receptor; +, positive; −, negative.
evaluation, and for the purposes of this study, outcome data for the 2 groups are considered together, as already mentioned. In 1 patient, suspicion of distant metastasis to the vertebra was histologically proven 3 weeks after diagnosis of primary breast cancer.

**Discussion**

Hormone therapy remains the mainstay for hormone receptor–positive breast cancer. The decision for hormone treatment has traditionally relied on assessment of ER and PR status of primary tumors, with the response generally related

<table>
<thead>
<tr>
<th>Survival</th>
<th>Mean (mo)</th>
<th>Median (mo)</th>
<th>Range (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free</td>
<td>46.1</td>
<td>32</td>
<td>0.7-175.4</td>
</tr>
<tr>
<td>Overall</td>
<td>154.3</td>
<td>—</td>
<td>11.6-186.5</td>
</tr>
<tr>
<td>After metastasis or recurrence</td>
<td>126.5</td>
<td>—</td>
<td>0.75-162.7</td>
</tr>
</tbody>
</table>

* As less than 50% of women had the event of interest for overall survival and survival time after metastasis and recurrence, the median survival statistics could not be computed.
† Three weeks after the primary diagnosis of cancer in the breast, the patient was histologically confirmed to have metastasis to the vertebra.

Image 31 Primary infiltrative ductal breast carcinoma (not otherwise specified) with positive cytoplasmic membrane staining for c-ERBB2 (A, H&E, ×200; B, ×400). The subsequent bone metastasis (C, H&E, ×400) was negative for c-ERBB2 (D, ×400).
suggest a wider range of discordance from 15.9% to 54% for ER and 14.2% to 44% for PR depending on the study and the technique used.

In recent years, the efficacy of trastuzumab in the treatment of metastatic breast cancers that overexpress c-ERBB2 has been proven, and it is the standard of care in the adjuvant setting. It has also been shown that the efficacy of trastuzumab is highly dependent on the c-ERBB2 status of the tumor. However, in the great majority of cases, c-ERBB2 status was determined on the primary tumor, and there are few published reports regarding the comparison of c-ERBB2 status between the primary and metastatic or locally recurrent sites.

Directly to ER and PR content. Patients with ER− and PR− tumors show virtually no response, whereas patients with breast cancers positive for both hormone receptors demonstrate a significantly higher response. Hormone receptor heterogeneity within the same tumor mass has been reported. For the most part, values reported were for dextran centrifugation techniques in earlier studies, with immunohistochemical analysis becoming routinely and widely used in the last decade. Previous discordance rates for simultaneous assays for ER varied from 12% to 39%, and PR discordance rates also ranged from 14% to 32%, although overall, the literature would seem to
The issue of whether ER, PR, and c-ERBB2 status should be reestablished in metastases and/or local recurrences has been debated, with some using results from the primary breast cancers to guide management when metastasis or local recurrence occurs. This view is based on the concept that expression of markers is assumed to reflect expression in the primary tumor. Because carcinogenesis is a multistep process, it is plausible that receptor expression may change when tumor progresses or as a result of treatment. Some studies have reported intratumoral heterogeneity, and it is, therefore, not surprising if such markers differ in metastases or local recurrences compared with the primary tumor. Several studies have been done to compare the ER expression in primary and corresponding metastatic or locally recurrent breast carcinomas. Some have included regional nodal and distant metastases as 1 group.\textsuperscript{33} Cell clones in metastatic tumors may differ from locally recurrent ones, and it was our intent to study these groups separately in detail. In many studies, ER and PR levels were measured by biochemical methods. A conclusion of positivity for such cases depends on tumor cellularity, and metastases with low cellularity may show false-negative results when using such techniques.

While studies using immunohistochemical analysis are also relatively scant,\textsuperscript{33} some had determined receptors

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image5.png}
\caption{In this primary breast infiltrative carcinoma (not otherwise specified), estrogen receptor immunohistochemical staining was negative (A, H&E, x400; B, x400), whereas the local recurrence was positive (C, H&E, x200; D, x200).}
\end{figure}
of primary breast cancers at the time of initial diagnosis and those of metastases at metastatic presentation.\textsuperscript{33,36,39} Therefore antibodies, techniques, interpretive criteria, and testing conditions may have differed in these paired primaries and metastases/recurrences. Only a few studies have compared c-ERBB2 status of the primary tumor with distant metastases.\textsuperscript{18,20,21} In the present study, we carried out immunohistochemical detection of ER, PR, and c-ERBB2 on primary tumors and their metastases and local recurrences at the same setting, using standardized protocols, antibodies, and diagnostic criteria.

Lower et al\textsuperscript{34} demonstrated 30% ER discordance and 19.5% PR discordance between primary and metastatic tumors by immunohistochemical analysis. Our study demonstrated 18% ER discordance (13/72) and 42% PR discordance (30/72) in metastatic lesions and 13% ER discordance (6/45) and 33% PR discordance (15/45) in locally recurrent lesions.

PR is a postreceptor marker for ER and, when present, signifies that the ER is functional.\textsuperscript{6,45} Hormone receptor discordance may reflect tumor dedifferentiation with development of metastasis or recurrence. Sequential breast cancer biopsies have shown that ER levels are reduced slightly with intervening endocrine therapy, although complete loss is uncommon. In contrast, PR levels decrease more dramatically during tamoxifen therapy, with up to half of tumors completely

\textbf{Image 6} Immunohistochemical staining for c-ERBB2 in the primary ductal carcinoma (not otherwise specified) was negative (A, H&E, ×200; B, ×200), and the local recurrence demonstrated positive reactivity (C, H&E, ×200; D, ×400).
losing PR expression when resistance develops. These ER− or PR− metastatic tumors then display a much more aggressive course after loss of hormone receptors compared with those retaining them, and patients then have a worse OS.46

The PR discordance rate was higher than ER discordance in our study and may imply a greater susceptibility of the post-ER pathway to expression changes as the tumor progresses. These hormonal receptor alterations may impact therapeutic strategies for metastatic/recurrent breast cancers, explaining clinical observations of visceral metastasis tending to be receptor-negative and less responsive to hormonal therapy.46

In our study, we found a greater proportion of conversion of ER and PR positivity in primary tumors to negative status in recurrences for women who received hormonal treatment.

The application of different immunohistochemical scoring methods potentially affects the rate of agreement in primary tumor vs locally recurrent and/or distant metastatic hormone receptor results. When the Allred scoring system was used, the level of agreement for ER between primary tumors and distant metastases diminished from substantial agreement with the method used in this study to moderate agreement with the Allred scheme, whereas that for PR remained within the same category of fair agreement. The level of agreement, however, improved between primary tumors and their local recurrences for ER and PR with the Allred scheme. Despite this, there remain differences in hormone receptor status that support a need for reassessment at recurrence, both local and metastatic.

Whether the defined threshold we used in this study for ER and PR positivity should be adjusted downward is a separate debate. In practice, apart from using the threshold that was previously referenced against the H score,1 we document the percentage of tumor cells stained and their staining intensity to provide maximal information to the managing oncologist.

The comparison of c-ERBB2 status in primary and metastatic/recurrent breast cancers has become an important issue in recent years owing to the development and approval of trastuzumab for the treatment of c-ERBB2–overexpressing metastatic and recurrent breast cancers. In the metastatic setting, in which the disease is virtually incurable, few drugs have shown a significant advantage, not only in terms of response rates but particularly in terms of OS. Trastuzumab, when given in combination with paclitaxel, achieved a survival benefit of 5 months compared with single-agent treatment of paclitaxel.47

Despite its benefit and although it is well tolerated, trastuzumab has a nonnegligible risk of cardiotoxicity. Because trastuzumab activity is directly dependent on the c-ERBB2 status of the tumor, careful selection of patients is crucial for increasing its clinical benefit and avoiding unnecessary treatment of patients who will most likely not benefit.

Several studies have compared c-ERBB2 expression of primary tumors and their distant metastasis.19,20,24,48,49
With cytogenetic analyses demonstrating potentially extreme genetic heterogeneity (up to 70% of polyclonality) in breast cancer, it is not surprising that the genetic composition of 31% of metastases differed almost completely from that of the paired primary tumors. Nevertheless, reported discrepancies for c-ERBB2 between primary tumors and metastases are low, with Gancberg et al indicating a 6% c-ERBB2 discordance by immunohistochemical analysis and 7% by FISH. Other studies with similar methods on bony tissue.

Among the distant metastases in our study, there was a significant proportion occurring to bone. Although it is possible that decalcifying procedures may have affected immunohistochemical results, we do not believe that it substantially alters the findings because we have observed not only negative receptors but also positive ones in bony metastases, and our laboratory, which also processes numerous bone marrow trephine biopsy specimens, has optimized immunohistochemical methods on bony tissue.

We observed a trend for patients with ER– metastatic and locally recurrent tumors to experience shorter survival time regardless of the primary tumor ER status. Although PR+ and PR– metastatic and locally recurrent tumors disclosed improved survival times in patients with originally PR+ primary tumors, there was no similar observation for cases that were initially PR–. In addition, patients with primary PR– tumors had reduced survival times even when their metastases and local recurrences were PR+. The data suggest that PR status of the primary tumor may be of more prognostic significance than that of the metastases and local recurrences.
the findings did not attain statistical significance, and it will be worthwhile to glean more information on larger cohorts with longer follow-up.

Our study shows immunohistochemical discordance of ER, PR, and c-ERBB2 status in metastases and local recurrences compared with their primary tumors. Although there was substantial agreement for ER and c-ERBB2 expression for metastases and their primary tumors and substantial and almost perfect agreement, respectively, for ER and c-ERBB2 for local recurrences and their primary cancers, there was significant disagreement for PR in both groups. It would be beneficial to routinely ascertain ER, PR, and c-ERBB2 status in metastatic and recurrent specimens for therapeutic and prognostic purposes.

References


