Receptor status (ER, PgR and HER2) discordance between primary tumor and locoregional recurrence in breast cancer

introduction
We report on three cases in which the HER2 status of a locoregional recurrence differed from that in the primary breast cancer. In one of these cases, estrogen receptor (ER) status also changed from primary to locoregional recurrence. All patients received neoadjuvant chemotherapy. Changes in HER2 and ER status between primary and metastatic breast cancer is a growing feature of the literature; however, most reports concern changes from primary to distant metastases, not from primary to locoregional recurrence. We briefly discuss the possible clinical significance of these changes and their possible therapeutic implications.

case 1
A 52-year-old woman presented with inflammatory breast cancer in March 2008. Pathological examination of Tru-Cut biopsy showed triple-negative [ER, progesterone receptor (PgR) and HER2 negative] ductal carcinoma of the right breast with Ki-67 35%. The patient received neoadjuvant epirubicin, cisplatin and fluorouracil for 6 months, followed by modified radical mastectomy in October 2008. The final pathological report showed no lymph node involvement and endocrine receptor-negative HER2 +3 cancer in the surgical specimen. The patient received postoperative locoregional radiotherapy followed by trastuzumab until September 2009.

In October 2009, she underwent resection of the right pectoralis major and surrounding soft tissue to remove recurrent disease. The pathology report showed triple-negative lesion with Ki-67 60%. She was given chemotherapy with cyclophosphamide, methotrexate and fluorouracil (classic CMF).

case 2
A 64-year-old woman presented with locally advanced breast cancer in August 2008. Diagnostic breast biopsy showed ductal carcinoma, ER and PgR 95%, HER2 +3, and Ki-67 32%. From November 2006 to April 2007, she received neoadjuvant anthracycline combination for four cycles followed by weekly paclitaxel and bevacizumab. In May 2007, she underwent right quadrantectomy, axillary dissection, and postoperative partial breast irradiation. Pathology was ypT3 (5.4 cm) pN2a (4/17), ductal carcinoma, ER and PgR positive, HER2 +1 by immunohistochemistry and negative by FISH. Metronomic chemotherapy continued from July 2007 to January 2008, adding trastuzumab in September 2007, which continued for a year. In February 2009, following suspicious ultrasonography, a mass was removed from the right axillary cavity, compatible with breast origin (ER 80% PgR 5%, HER2 +2 by immunohistochemistry, negative by FISH). The patient was started on aromatase inhibitor and capecitabine.

case 3
A 52-year-old woman presented with locally advanced right breast cancer (cT3cN1M0) in October 2006. Diagnostic breast biopsy showed ductal carcinoma, ER and PgR negative, HER2 +3, and Ki-67 32%. From November 2006 to April 2007, she received neoadjuvant anthracycline combination for four cycles followed by weekly paclitaxel and bevacizumab. In May 2007, she underwent right quadrantectomy, axillary dissection, and postoperative partial breast irradiation. Pathology was ypT3 (5.4 cm) pN2a (4/17), ductal carcinoma, ER and PgR negative, HER2 +1 by immunohistochemistry and negative by FISH. Metronomic chemotherapy continued from July 2007 to January 2008, adding trastuzumab in September 2007, which continued for a year. In February 2009, following suspicious ultrasonography, a mass was removed from the right axillary cavity, compatible with breast origin (ER 80% PgR 5%, HER2 +2 by immunohistochemistry, negative by FISH). The patient was started on aromatase inhibitor and capecitabine.

discussion
Early studies reported that HER2 expression was stable over time and at multiple metastatic sites in breast cancer patients [1]. As a result, routine determination of HER2 in metastases was not recommended [2]. More recently, retrospective analyses have reported increasing discordance of HER2 status between primary and metastatic sites. The retrospective study of Lower et al. [3], the largest so far published, analyzed HER2 status in 382 metastatic breast cancer patients, reporting discordance between the primary and subsequent metastatic cancer in 33.2% of cases, with change from positive to negative in 23.6% and change from negative to positive in 9.6%. Other studies have reported hormone receptor status discordance...
rates of 28%–21% between primary and metastatic breast tumor [4, 5]. In all these studies, most comparisons regarded primary with distant metastatic sites, very few concerned primary versus locoregional recurrence.

Our three cases are singular as they document discordance between the primary tumor and locoregional recurrence, as summarized in Table 1.

The mechanisms of change of hormone receptor and HER2 expression have not been explicitly studied. Chemotherapy may eliminate certain subclones of tumor cells, selecting others that dominate in the recurrent disease [6]. In our cases, all changes occurred after chemotherapy. Receptor status may also depend on the analytical method used. We suggest that hormone receptor and HER2 status should be determined for recurrences, if technically feasible and not excessively invasive; any change identified may enlarge treatment possibilities for the patient and improve selection for targeted therapies. This is particularly important for locoregional recurrence after mastectomy, which carries an unfavorable prognosis with high risk of distant metastases [7].

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**References**


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<tr>
<th>Site</th>
<th>ER status</th>
<th>HER2 status</th>
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<tbody>
<tr>
<td>Case 1</td>
<td>Primary: diagnostic biopsy</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Primary: final surgery</td>
<td>Negative</td>
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<tr>
<td></td>
<td>Locoregional recurrence</td>
<td>Negative</td>
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<tr>
<td>Case 2</td>
<td>Primary: diagnostic biopsy</td>
<td>Positive</td>
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<td></td>
<td>Primary: final surgery</td>
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<td></td>
<td>Locoregional recurrence</td>
<td>Positive</td>
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<tr>
<td>Case 3</td>
<td>Primary: diagnostic biopsy</td>
<td>Negative</td>
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<tr>
<td></td>
<td>Primary: final surgery</td>
<td>Negative</td>
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<td></td>
<td>Locoregional recurrence</td>
<td>Positive</td>
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ER, estrogen receptor.