Introduction:
The management of breast cancer has evolved over recent years to allow for more tailored therapies based on the biological characteristics of the primary disease such as the estrogen receptor (ER), progesterone receptor (PR) and HER2-neu receptor (HER2) status. Despite the advancements made in the adjuvant treatment of breast cancer, however, over 20% of patients will develop metastatic disease (1). Historically, clinicians treated these metastatic patients based on the biology of the primary cancer but evidence has suggested that a significant proportion of metastases may undergo a change in hormone receptor and HER2 receptor status from the original breast cancer, which in turn may have implications for management strategy.

Target Population:
These recommendations apply to patients, with a history of primary cancer of the breast, who are suspected of having metastatic/recurrent breast cancer.

Questions:
1. Should all patients, with a history of breast cancer, suspected of developing a recurrence/metastases undergo a biopsy (where feasible) and retesting of ER, PR and HER2 status?
2. How could biopsy and retesting result in the change of treatment options for patients with recurrent/metastatic disease?

Supporting Evidence:
Though retrospective data have indicated discordance between the tumor biology of primary and metastatic breast cancer for many years, such discordance was believed to be related to the limitations of the retrospective evidence, sampling errors in focally receptor-positive cancers, as well as a lack of accuracy and limited reproducibility with the receptor assays (2). Therefore, treatment
decisions were based on the biology of the primary breast cancer. Occasionally, biopsy was performed for confirmatory purposes in local recurrences but rarely, if ever, for distant ones.

Recent prospective data, however, have suggested that a genuine change may occur in the biology of the disease in patients with metastatic disease thereby creating the possibility that some of these patients may be offered alternative treatment. Discordance has been recorded for ER and PR results between the primary breast cancer and the metastatic disease in approximately 20% to 50% of patients studied (3-9). In the case of hormonal receptors, a larger proportion of identified changes are from positive to negative in both ER and PR, though a significant number can change from negative to positive (10-13). The receptor status of the metastatic disease has also been shown to influence survival, with the median survival for patients with ER-negative relapsed disease to be significantly shorter than those with ER-positive disease (11,12,14). The American Society of Clinical Oncology (ASCO) in cooperation with the College of American Pathologists (CAP) have recommended in their 2010 guideline, that ER and PR status be determined, not only on invasive breast cancers, but all breast cancer recurrences as well (15).

The discordance rate for HER2 between primary breast cancer and metastatic disease is reported as being between 6% and 30% (3,6,16-18). The ASCO-CAP 2013 recommendations state that HER2 status should be determined in all patients with invasive breast cancer, whether early stage or recurrent disease (19). Switching from HER2 positive in the primary cancer to negative in the metastatic disease, and negative in the primary to positive in the metastatic disease has also been reported in the data (16-18,20). A switch from positive HER2 status to negative may have some prognostic importance as there is evidence to suggest that it is associated with decreased survival (17,21-25). Conflicting evidence has been reported on whether when multiple metastatic sites are tested for HER2 using fluorescence in situ hybridisation (FISH), that discordance may be found among the metastatic sites (16,26).

Knowing that discordance may exist between primary and metastatic cancers of the breast is important, but more so if this knowledge can be used to alter the clinical management of the patient. Recent studies indicated that 12% to 20% of those patients with pathologically confirmed discordance had a change in their treatment plan, such as endocrine therapy, trastuzumab, and/or chemotherapy, based on the results of the biopsy (3,6,13,14,27). A large pooled analysis of two recent prospective studies, reporting on the ER/PR/HER2 receptors in matched primary and metastatic (either local or distant) breast cancer, included the United Kingdom’s Breast Recurrence In Tissues Study (BRITS) and the Canadian DESTINY study (6,13,28). The authors reported that the usual reasons for a treatment plan alteration was a change in HER2 status, gain of hormone receptor, the identification of a benign lesion or a second malignancy. One prospective study found that 10% of patients suspected of having metastatic breast cancer, were subsequently found to have either benign disease or another malignant process (3). Therapy was most often changed when there was an apparent gain of a receptor, allowing for the introduction of other treatment options such as endocrine therapy or trastuzumab. The recent GEICAM 2009-03 ConvertHER study, the largest prospective trial of its kind, which evaluated conversion rates of ER/PR/HER2 receptors was the only study that compared the expression results of 31 local laboratories to those obtained at a single central laboratory (9). Though the conversion rates were lower at the central lab as compared with local labs, the discrepancies in receptor results (ER 13% vs 21%, PR 28% vs 35%, HER2 3% vs 16% respectively) were similar to those found in the pooled analysis of the BRITS and DESTINY studies described above. This trial found 4% of patients also had a clinical misdiagnosis of recurrent breast cancer. Though lower than the 10% reported above, it still highlights the importance of biopsy for differential diagnosis.
One of the DESTINY study’s investigational endpoints was to assess the impact of discordance on patient management and survival (6). It found that if treatment was altered according to discordant results between primary and metastatic disease, there were no apparent differences in TTF (time to treatment failure) or OS (overall survival) between patients with concordant and discordant disease. The authors did admit that the power of their study to detect such differences were low. Retrospective studies, however, have shown with consistency that poorer survival has been found to be associated with positive to negative ER switches and a lower likelihood of responding to anti-hormonal therapy (11,12,14,29,30). Data from retrospective studies found a similar trend of shorter overall survival for patients whose HER2 status switched from positive to negative compared to patients that switched from negative to positive or were concordant (16,24,25).

The potential benefits of having patients with a history of breast cancer, undergo a biopsy of suspected recurrent or metastatic disease include:

- Identification of benign lesions that may have been assumed to be metastatic;
- Identification of a second malignancy unrelated to original breast cancer requiring a different plan of care;
- Provision of more accurate treatment regimens if discordant results are found;
- Allows clinicians to more accurately discuss prognosis with the patient allowing more informed treatment decisions in conjunction with maintaining quality of life.

In the pooled analysis, the authors concluded that biopsy of recurrent disease and the ensuing discordant results would cause clinicians to modify the choice of therapy once for every 7 biopsies of recurrent disease performed (13). Receptor discordance has been reported in one prospective study to be more frequently found in distant metastases when compared to locoregional recurrences, but much data to the contrary also exists (6,28,31,32).

**Technical Issues**

- Older retrospective studies on discordance in hormone receptor and HER2 status used older pathological techniques, utilized different staining procedures or included heterogeneous groups of patients including those with local recurrences (3);
- Currently, immunohistochemistry (IHC) is routinely used for hormone receptor analysis. Technical issues with IHC, related to specimen analysis, have been encountered with fixation, paraffin storage times, and variation in staining methodology that may create a false discordance (4,33);
- FISH is more sensitive and specific for testing HER2 status than IHC but variations exist within this testing method as well (16);
- Extensive studies have been conducted on the use of core needle biopsy (CNB) in accurately determining the ER and HER2 status of breast cancer. However, caution needs to be exercised in considering PR results which have a higher degree of discrepancy/variability (34);
- Fine needle aspirations (FNA), though frequently used to confirm metastatic disease, may be less reliable than CNB for ER determination (35);
- Presently, it remains unclear whether prior exposure to systemic therapy may alter, to some degree, the emergence of heterogeneous clones which may bring about molecular biomarker discordance (8).

Bone-only metastatic disease from a breast primary may be problematic in terms of obtaining accurate ER, PR and HER2 results from a CNB. The tissue obtained from the biopsy requires decalcification and the acid-based solution used to do this, also reduces the immunoreactivity of most antigens which limits an accurate assessment of the receptors (36).
**Recommendations:**

- Where feasible, all patients with a history of breast cancer, suspected of having recurrent/metastatic disease should undergo a biopsy and retesting for the presence of ER, PR, and HER2 receptors;
- For patients who have an apparent gain of a receptor following testing, a physician-patient discussion should occur regarding the implications for management strategies;
- Despite the lack of evidence to suggest an improvement in progression-free survival (PFS) or OS with the addition of anti-hormonal and/or anti-HER2 therapy for those with receptor gain, the poorer expected prognosis for these patients suggests that doing so would be a reasonable approach.

**Note:** At present, there is not enough evidence to support the discontinuation of endocrine therapy or HER2 directed therapy in patients with an apparent loss of a receptor.

**Search Strategy:**

Literature searches were conducted in PubMed, Embase, and the Cochrane Library, using keywords “discordance” AND “breast” AND “neoplasms” AND “primary” AND “metastases” AND “estrogen receptor” AND/OR “progesterone receptor” AND/OR “HER2 receptor”, as well as an extensive manual search of the reference lists of available literature articles. Guideline searches were also carried out on the websites of the world’s most highly respected cancer organizations and agencies. All selected literature articles and source guidelines were in English and dated after the year 2000 (unless the selection was an earlier landmark study) up to April 2014. The inclusion/exclusion process consisted of selecting guidelines from reputable cancer organizations with preference given to those from Canadian sources where possible. Five source guidelines were identified and conformed to our search criteria, which were selected due to currency, quality of content and/or were Canadian in origin (37-41).

The five selected source guidelines were put through the ADAPTE process (42) with an AGREE assessment (43), and the NCCN “Breast Cancer” guideline was chosen to be adapted for use in our guideline (40). The NCCN guideline was selected as the optimal choice due to its applicability, quality and currency of content.

There has been much debate but no consensus on the ‘grading of evidence’ in Canada. Presently, Canadian experts in the field of guideline development are involved in an ongoing in-depth analysis of the functionality of grading. Until such time as a report is released of their findings, and a consensus reached on whether to assign a grade of recommendation to a guideline, this group has decided to forgo the use of grading.

No competing or conflicts of interest were declared.

**Disclaimer:**

These guidelines are a statement of consensus of the Breast Disease Site Group regarding their views of currently accepted approaches to diagnosis and treatment. Any clinician seeking to apply or consult the guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment.
Contact Information:

For more information on this guideline, please contact Dr. Erin Powell MD FRCPC, Dr. H. Bliss Murphy Cancer Center, St. John’s, NL; Telephone 709-777-7802. For the complete guideline on this topic or for access to any of our guidelines, please visit our Cancer Care Program website at www.easternhealth.ca

Literature Support:

Clinical Practice Guidelines - Breast Disease Site

**Guideline Title:** Molecular Biomarker Discordance between Primary and Recurrent/Metastatic Breast Cancer.

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34. Arnedos M, Nerurkar A, et al. Discordance between core needle biopsy (CNB) and excisional biopsy (EB) for estrogen receptor (ER), progesterone receptor (PgR), and HER2 status in early breast cancer (EBC). 2009;20(12):1948-1952.

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