CANCERCare
A PROGRAM OF EASTERN HEALTH

Clinical Practice Guidelines - Breast Disease Site

Guideline Title:	Molecular Biomarker Discordance between Primary and Recurrent/Metastatic Breast Cancer - **Summary**	**Date:**	**(O):** **(R):**	Apr 30, 2014
Tumor Group:	Breast Disease Site Group	**Page:**		1 of 4
Issuing Authority:	Dr. Jehann Siddiqui Clinical Chief, Cancer Care Program	**Date Signed:**		July 10, 2015
Adapted From:	National Comprehensive Cancer Networks' "Breast Cancer" guideline, April 2014 (1).			

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.

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.

Supporting Evidence:

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 (2-6). A large pooled analysis of two recent prospective studies, reporting on the ER/PR/HER2 receptors in matched primary and recurrent breast cancer, included the United Kingdom's Breast Recurrence In

Tissues Study (BRITS) and the Canadian DESTINY study (2,3,7). 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 (2). 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 (8). Though the conversion rates were lower at the central lab when 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 (3). It found that if treatment were 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 (5,9-12). 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 (13-15).

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 (16).

Qualifying Statements:

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.

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:

1. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Breast cancer. April 2014. www.nccn.org
2. Simmons C, Miller N, et al. Does confirmatory tumor biopsy alter the management of breast cancer patients with distant metastases? Ann Oncol. 2009;20(9):1499-1504.
3. Amir E, Miller N, et al. Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. J Clin Oncol. 2012;30(6):587-592.
4. Amir E, Clemons M, et al. Tissue confirmation of disease recurrence in breast cancer patients: Pooled analysis of multi-centre, multi-disciplinary prospective studies. Cancer Treat Rev. 2011, doi:10.1016/j.ctrv.2011.11.006.
5. Pushpalatha KA, Idirisinghe MBBS, et al. Hormone receptor and c-ERBB2 status in distant metastatic and locally recurrent breast cancer. Am J Clin Pathol. 2010;133:416-429.
6. Curigliano G, Bagnardi V, et al. Should liver metastases of breast cancer be biopsied to improve treatment choice? Ann Oncol. 2011;22(10):2227-2233.
7. Thompson AM, Jordan LB, et al. Prospective comparison of switches in biomarker status between primary and recurrent breast cancer: The breast recurrence in tissues study (BRITS). Breast Cancer Res. 2010;12(6):R92.
8. De Dueñas EM, Hernández AL, et al. Prospective evaluation of the conversion rate in the receptor status between primary breast cancer and metastasis: Results from the GEICAM 2009-03 ConvertHER study. Breast Cancer Res Treat. 2014;143
9. Lower EE, Glass EL, et al. Impact of metastatic estrogen receptor and progesterone receptor status on survival. Breast Cancer Res Treat. 2005;90:65-70.
10. Lindström LS, Karlsson E, et al. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. J Clin Oncol. 2012;30(21):2601-2608.
11. Liedtke C, Broglio K, et al. Prognostic impact of discordance between triple-receptor measurements in primary and recurrent breast cancer. Ann Oncol. 2009;20(12):1953-1958.
12. Kuukasjärvi T, Kononen J, et al. Loss of estrogen receptor in recurrent breast cancer is associated with poor response to endocrine therapy. J Clin Oncol. 1996;14(9):2584-2589.
13. Gancberg D, Di Leo A, et al. Comparison of HER-2 status between primary breast cancer and corresponding distant metastatic sites. Ann Oncol. 2002;13:1036-1043.
14. Wilking U, Karlsson E, et al. HER2 status in a population-derived breast cancer cohort: discordances during tumor progression. Breast Cancer Res Treat. 2011;125:553-561.

15. Niikura N, Liu J, et al. Loss of human epidermal growth factor receptor 2 (HER2) expression in metastatic sites of HER2-overexpressing primary breast tumors. J Clin Oncol. 2011.doi:10.1200/JCO.2010.33.5232.
16. Khasraw M Brogi E, et al. The need to examine metastatic tissue at the time of progression of breast cancer: Is re-biopsy a necessity or a luxury? Curr Oncol Rep. 2011;13:17-25.