

# Advances in treatment and care in metastatic breast cancer (MBC): are there MBC patients who are curable?

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**Abstract:** Metastatic breast cancer (MBC) remains a largely incurable disease. The goals of treatment for MBC are still to maintain quality of life and prolong survival. However, some cases of MBC with a long-term relapse free survival occurs, implying that a small subset of MBC patients could become curable. Although it is a controversial issue of whether MBC can be cured, a more aggressive multidisciplinary approach to MBC with a curable intent may help improve MBC patient outcomes. The Earlier detection of metastatic disease by using modern imaging technologies may allow the detection of metastasis before cancer cells spread widely. This brief review focuses on the potentials of clinical response at initial therapy of MBC and early detection of metastatic disease of the possibility of cure of MBC patients.

**Keywords:** Oligometastasis (OM); early detection; metastatic breast cancer (MBC); clinical complete response

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## Introduction

Breast cancer is the second most common cancer in the world and the most frequent cancer among women. with approximately 1.7 million new cancer cases diagnosed yearly (1). Despite improvements in the early detection of breast cancer and the development of more effective systemic therapies, about 30% of patients with early disease will relapse with distant metastases (2), and metastatic disease remains the leading cause of death in those patients with breast cancer (3). Rapid evolution of targeted therapies and understandings of molecular biology and genetics of breast cancer have improved metastatic breast cancer (MBC) outcomes in recent years (4,5), however, many physicians still believe that the metastatic disease remains largely incurable, and the goals of treatment for MBC are to delay disease progression and to prolong survival with maintaining a good quality of life. However, many physicians also experience

that it is possible to obtain long-term survival using standard treatments in a small number of cases (6).

## Molecular subtypes and clinical complete response (CR)

Trastuzumab has significantly improved survival of patients with HER2-positive MBC (7). We especially experience the case with a high probability of being curable disease in patients with HER2-positive MBC. There have been several reports of durable clinical CR with HER2-positive MBC treated with anti-HER2 therapy (8-10). Niikura *et al.* (11) assessed 108 HER2-positive MBC patients who received trastuzumab for more than 2 years as the first-line treatment. They showed that more than 80% of patients survive 10 years after the diagnosis of MBC, and more than half of patients achieved clinical CR. And they also showed that 21 patients with CR had not experienced disease

progression even after the interruption of trastuzumab therapy. Gullo *et al.* (12) showed 6 of 13 cases with achieving CR after receiving trastuzumab together with their first-line chemotherapy remain alive and continuously cancer free. Witzel *et al.* (13) identified 268 patients with HER2-positive MBC who had not progressed for at least 2 years on trastuzumab. They showed that 47.1% of patients remained in remission for more than 5 years, and achieving CR after initial trastuzumab treatment was one of the factors associated with longer time to progression. Yeo *et al.* (14) reported 25 HER2-positive MBC patients who remained in remission more than 5 years, and showed a trend towards improved PFS in those patients who achieved CR. These data may indicate that a small proportion of patients with HER2-positive MBC have a potential of cure, and also suggest that achieving clinical CR with first-line therapy is important for durable CR. Moreover, Rahman *et al.* (15) showed that the outcome of MBC patients obtaining clinical CR with first-line doxorubicin-containing chemotherapy was better than for patients without clinical CR. Therefore, achieving clinical CR with initial treatment may be one of the goals of MBC patients. It is notable that the rate of clinical CR is much higher in patients with HER2-positive MBC than other molecular subtypes. However, even MBC with other molecular subtypes (6), there may be a potential of cure if clinical CR can be achieved at initial treatment with effective combination of chemotherapy and targeted therapy.

### Oligometastasis (OM)

The MBC patients with OM, which is characterized by solitary or few detectable metastatic lesions, has been identified approximately 1–10% of newly diagnosed patients with stage IV disease, and are potentially curable (16,17). It is currently unclear whether radical local therapy for OM is beneficial or not, however, a more aggressive and multidisciplinary approach before the cancer cells spread widely could lead to be curable. Kobayashi *et al.* (18) identified 75 cases with OM breast cancer in their 30-year experience, and showed a 10-year overall survival rate (OSR) of 59.2% and a 10-year relapse-free rate (RFR) of 27.4%. They also showed that the cases with only single organ involvement were associated with a better survival (a 10-year OSR of 73% and a 10-year RFR of 42%) and the cases achieved CR by multidisciplinary treatments survived longer than the cases with partial response or stable disease. Hanrahan *et al.* (16) summarized the outcomes of

Stage IV breast carcinoma with no evidence of clinically measurable disease by surgical resection and/or irradiation with curative intent in four phase II trials. They showed a 5-year disease-free survival (DFS) of 34% and 5-year OS of 59% in the docetaxel-based trial, and showed both 20-year DFS and OS of 26% in the 3 doxorubicin-based studies. The European School of Oncology-Metastatic Breast Cancer (ESO-MBC) Task Force stated in their consensus recommendations; “*A small but very important subset of MBC patients, for example, those with a solitary metastatic lesion, can achieve complete remission and a long survival. A more aggressive and multidisciplinary approach should be considered for these selected patients. A clinical trial addressing this specific situation is needed.*” (17). However, early detection of patients with OM which considered as an intermediate biological state between localized and widely metastatic disease is challenging. Surveillance guidelines (19,20) for breast cancer patients after surgery recommend regular follow-up with mammography, history, and physical examination, but additional routine laboratory or radiographic investigations for asymptomatic patients are not recommended because there is no evidence of improved clinical outcomes associated with the early detection of distant metastasis. However, the recommendations of these guidelines were based on data from clinical trials reported in the 1990s (21,22). Recent advances in imaging technologies including, for instance, helical CT, bone scintigraphy, PET and MRI allows the very early detection of distant metastases. Therefore, more intensive postsurgical surveillance with using modern imaging technologies may improve early detection of distant metastases, especially in patients with high-risk breast cancer. In Japan, we currently started a prospective randomized Phase III trial (23) for confirming to the superiority of intensive follow-up in terms of OS over standard follow-up in high-risk breast cancer patients. The intensive follow-up group undergo physical examination, bone scintigraphy, chest computed tomography, abdominal computed tomography, brain magnetic resonance imaging/computed tomography and frequent tumor marker evaluations, whereas the standard follow-up group undergo physical examination at the same frequency and tumor markers will be evaluated once a year.

### Conclusions

The rapid advances in molecular biology and evolving treatment options have led to the improvement of survival in patients with MBC. As we indicated, there is reasonable

evidence to suggest that some MBC patients could be cured, although it is currently still a small number. MBC is considered generally incurable, but we believe there are the patients who can aim to cure. Advances in treatment based on understanding of molecular biology could offer the attainment of clinical CR with first-line treatment of MBC patients and may provide the patients with possibility of cure. Advances in imaging technologies could offer the study aimed at a cure of early MBC. In the future, new strategies for MBC could standardize with a curable intent.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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