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# Letter to the Editor

## In Reply: Local Therapy in Stage IV Breast Cancer Patients

*To the Editor:*

I would like to thank Dr. Fitzal for his letter regarding the editorial "Primary Tumor Resection in Stage IV Breast Cancer: Consistent Benefit or Consistent Bias?"[1] Dr. Fitzal highlights the issue of the timing of surgical therapy for the primary tumor in the setting of metastatic disease and presents the rationale for tumor resection prior to systemic therapy, pointing to the "self-seeding" hypothesis of Norton and Massague.[2] This hypothesis, although intriguing and well-founded, still awaits empirical support. As defined so far, it includes the concept that metastatic sites also seed and reseed, so that if effective systemic therapy is not available, continued propagation of new metastases and growth of existing metastases would occur even if the primary tumor has been removed. We would therefore adhere to the idea that resection of a primary tumor will help only those women with clinical metastases whose tumors have demonstrated responsiveness to systemic therapy. For those women who progress on state-of-the art systemic treatment, the prognosis is poor indeed, and until a systemic regimen is identified that controls the metastatic sites, resection of the primary can have no salutary effects (other than palliation of symptoms for those who need it).

In support of this proposed sequence of treatment, a recent analysis of timing of surgery by Rao et al. divided 75 women with Stage IV breast cancer at presentation into three groups: those who underwent resection of the primary tumor within three months of diagnosis, those operated on 3–9 months from diagnosis, and those receiving surgical therapy more than 9 months from diagnosis.[3] Although the authors did not stratify women by whether surgery was used prior to or following systemic therapy, they acknowledge that the early surgery group probably received surgery as the first treatment modality (prior to diagnosis of metastatic disease), whereas the later surgery groups probably received surgery following systemic therapy. Women who received primary tumor resection in the later time intervals (i.e., 3 months or longer after diagnosis) experienced a significantly longer progression-free survival than those who were operated on prior to diagnosis.

Dr. Fitzal also points out that a compelling biological rationale for therapy to the primary tumor in the metastatic setting is still lacking; while this is in large part true, there are several possibilities in addition to the self-seeding[2] and stem cell[4] hypotheses referred to by Dr. Fitzal. These include the priming of premetastatic niches by cytokines released by the primary tumor;[5] or a potential immune-suppressive role of the primary tumor.[6] Additionally, recent exciting work by Weinberg and colleagues represents an attempt to distinguish between the metastatic capacity of primary tumors and metastatic lesions.[7] Here, poorly metastatic breast cancer cells implanted subcutaneously into immunocompromised mice metastasized efficiently to the lungs only when admixed with mesenchymal stem cells from the bone marrow. In this model, mesenchymal stem cells appear to populate the primary tumor site far more efficiently than they populate metastatic sites in the lung, suggesting that the admixed mesenchymal stem cells exert their prometastatic effects primarily in the context of the primary tumor. Additional laboratory investigation that focuses on the possibly distinct roles of the primary tumor and metastatic lesions in the propagation of disseminated disease are badly needed and hopefully will be undertaken along the classic paradigm of translational research: in this case, bedside to bench, with the expectation that we will return to the bedside with an improved understanding of the forces driving metastatic progression.

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