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EDITORIAL – BREAST ONCOLOGY

De Novo Stage 4 Metastatic Breast Cancer: A Surgical Disease?

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The diagnosis for 6% of new breast cancer cases each year in the United States is de novo metastatic disease or stage 4 at presentation. Although treatment for these patients is largely centered around systemic therapy, with local therapy (surgery and/or radiation therapy) largely reserved for palliation, it has been postulated that resection of the primary breast cancer may improve survival. This controversy is illustrated by the National Comprehensive Cancer Network (NCCN) guideline, which states, "the role and timing of surgical removal of the primary (breast cancer) in patients presenting with de novo stage IV disease is the subject of ongoing investigations."

The rationale for proceeding with surgical intervention includes the possibility of increasing immunomodulation and chemotherapy effectiveness through decreased tumor burden, decreasing metastatic potential by eliminating breast cancer stem cells, disrupting the seeding potential of new metastases, and decreasing the likelihood of resistant disease. On the other hand, it has been argued that surgical intervention may result in delayed administration of systemic therapy, surgical morbidities, loss of the primary cancer as a marker of disease response, and disruption of cytokines that may restrict the growth of distant metastases.

A review of retrospective studies on the management of de novo metastatic breast cancer has largely shown mixed findings, with some studies reporting an improved overall survival (OS) of 1–2 years with surgical intervention.[1–5] However, the patients in the surgical group often were younger and had less metastatic disease burden. Other retrospective studies accounting for selection bias in the surgical group, mainly through matched pair analysis, show this survival benefit to be no longer apparent,[6–8] highlighting the need for randomized prospective trials.

In December of 2013, two prospective randomized trials led by Soran et al.[9] (Turkey) and Badwe et al.[10] (India) were introduced through oral presentations at the San Antonio Breast Cancer Symposium. The prospective trial by the Tata Memorial Center conducted by Badwe et al.,[10] which evaluated the effect that removal of the primary tumor and axillary lymph nodes has on OS and progression-free survival, was subsequently published in 2015.[11] The study randomized 350 patients between 2005 and 2013 based on site of distant metastases, number of metastatic lesions, and hormone receptor status. The patients with a resectable primary breast cancer that could be treated with endocrine therapy were assigned up front, whereas those with unresectable metastatic disease were treated with chemotherapy before randomization (which was then based on objective tumor response to chemotherapy). Notably, the patients with human epidermal growth factor 2 (HER2)-positive disease were not treated with HER2-directed therapy, which would not be considered standard of care in most developed countries. Badwe et al.[10] reported that locoregional resection of the primary tumor did not increase OS for the patients who had responded to frontline chemotherapy.

Unlike the findings of the Tata Memorial Center, Soran et al., in this current issue of *Annals of Surgical Oncology,* present the first randomized study to show a statistically significant improvement in median survival with surgery for patients with de novo stage 4 breast cancer at the 5-year follow-up assessment.[9]

In this multicenter, phase 3, randomized control trial (MF07-01), conducted in Turkey, which compared locoregional treatment (LRT) or surgery followed by systemic therapy (ST) versus ST alone for naïve stage 4 breast cancer patients, Soran et al.[9] reported a reduction in the hazard of death for 34% of the former group at 40 months

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(hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.49–0.88; $p = 0.0050$). This reduced hazard of death was not evident in a shorter follow-up period of 36 months with a median follow-up period of 54.5 months. Interestingly, by the fifth year of follow-up evaluation, 41.6% (95% CI, 32.5–50.4) of the patients were alive in the LRT group versus 24.4% (95% CI, 16.9–32.6) in the ST group ($p = 0.005$). This study included 274 patients, and most of the LRT patients (102/138, 74%) underwent a mastectomy and axillary lymph node dissection, with ST started approximately 27.1 ± 9.9 days after surgery. The ST regimens, including chemotherapy and bisphosphonates, were similar between the two groups ($p > 0.05$). In the LRT group, 38% of the patients received post-mastectomy radiation therapy (PMRT), and the median survival did not differ between the patients with PMRT and those without PMRT ($p = 0.36$). In addition, the rates of irradiation and surgical intervention to metastatic sites were similar between the two groups ($p = 0.07$).

Although the study's primary aim was to assess LRT efficacy in relation to OS, unplanned subgroup analyses showed OS to be longer for the LRT group with respect to estrogen receptor (ER)/progesterone receptor (PR) plus disease (HR, 0.63; 95% CI, 0.44–0.89; $p = 0.008$), HER2/neu(–) (HR, 0.64; 95% CI, 0.45–0.91; $p = 0.01$), age younger than 55 years (HR, 0.57; 95% CI, 0.38–0.86; $p = 0.007$), and solitary bone-only metastasis (HR, 0.47; 95% CI, 0.23–0.98; $p = 0.04$). These findings are similar to those reported in prior meta-analyses, such as the studies by Harris et al.[12] and Petrelli and Barni.[13] Another secondary end point investigated by Soran et al.[9] was the rate of locoregional progression/recurrence, defined as clinically or radiographically documented size progression of the primary tumor, ulceration, bleeding, fungation, or findings of new locoregional lesions. The authors state that the rate was 11 times higher in the ST group. Another secondary end point studied was 30-day mortality, which did not differ between the groups (LRT, 1.4%; ST, 1.5%).

Although these findings challenge current standards of care for patients with de novo stage 4 breast cancer in terms of limiting surgical intervention to palliation, this trial had several significant limitations. The study design was based on the assumption of a 3-year OS of 35% in the LRT group and 17% in the ST group from literature published before 2007. As recognized by the authors of this study, recent improvements in systemic treatment, including targeted therapy, have markedly increased the 3-year survival for patients. With better systemic therapy regimens, the perceived surgical benefits in terms of median survival rates reported by Soran et al.[9] may be diminished. Furthermore, stratification factors such as patient age, tumor size, histologic grade/type, and receptor status, which are critical to randomization, were not planned. Instead, Soran et al.[9] used a nonstandard statistical justification, which they argued was based on treatment-effectiveness analysis adjusted for covariates by use of multivariate analysis after stratification. It is also important to note that the LRT group had higher rates of ER/PR-positive disease (85.5% vs. 71.8%; $p < 0.05$) and lower rates of triple-negative disease (7.3% vs. 17.4%; $p < 0.05$). Therefore, the patients in the LRT group most likely had less aggressive disease. It also was discussed that among patients with triple-negative breast cancers, the median survival was 17.5 months in the LRT group and 18 months in the ST group (HR, 0.74; 95% CI, 0.32–1.75; $p = 0.49$). Given that the ST group had more patients with triple-negative breast cancer, this likely also contributed to the reported difference in survival outcomes. In addition, when the 3-year survival of the patients with multiple pulmonary/liver metastases was analyzed, the LRT group showed a markedly lower survival (31%; 95% CI, 9–55%) than the ST group (67%; 95% CI, 38–85%) ($p = 0.05$). Furthermore, solitary bone metastasis was not confirmed by biopsy, but instead, the diagnosis was based on two imaging methods, namely, whole-body scintigraphy and FDG-PET/CT. Finally, it is difficult to discern whether the issue of lead time bias was addressed by Soran et al.[9] Some patients in the trial likely had a shorter time from metastatic diagnosis to treatment, whereas other patients may have had metastatic disease for a longer period.

The MF07-01 study findings have important implications by further emphasizing the complexity and heterogeneity of breast cancer biology. Like prior studies, the findings of Soran et al.[9] continue to show that patients with de novo stage 4 metastatic breast cancer who present with triple-negative disease and/or pulmonary or liver metastases will not benefit from LRT. Patients who did benefit from LRT were younger women who mainly had ER+/PR+/HER2/neu(–) disease. It is difficult, however, to attribute the survival benefit in this group to surgical intervention because this group inherently had more favorable disease. Soran et al.[9] have not provided definitive support for surgical intervention as a means to improve survival for patients who present with de novo metastatic breast cancer. Therefore, these cases should continue to be discussed in a multidisciplinary fashion.

In the United States, overall breast cancer death rates, as reported by the American Cancer Society, declined rapidly from 2006 to 2015, with a total decline of 39% through 2015, and this is largely attributed to both early screening and improved systemic therapy (mainly the introduction of targeted therapies such as endocrine and HER2-based regimens). As such, it would be difficult not to initiate systemic therapy up front for patients with de novo metastatic breast cancer. One such study, which addresses the role of systemic therapy followed by surgical intervention

in this subgroup, is the United States-based Translational Breast Cancer Research Consortium (TBCRC) 013 trial, a prospective registry trial that enrolled 112 patients with an intact primary tumor between 2009 and 2012 at 14 institutions.[14] After the patients had received first-line therapy by their treating providers, all the responders (94 patients, 85%) were considered for elective surgery. A multivariable analysis, with censorship for survival at 6 months, showed that surgery of the primary cancer did not improve overall survival among the responders, who had a median survival of 71 months versus 65 months for the patients without surgery (or 30-month survival rates of 77 and 76%, respectively; $p = 0.85$). These initial findings of the TBCRC 013 study must be addressed because the benefits outlined by Soran et al.[9] are for patients who are treatment *naïve* before surgery.

Given the rapid advances in systemic therapy, it is difficult to envision not initiating patients on a first-line systemic therapy before surgery, thereby rendering the findings of Soran et al.[9] less relevant in this clinical setting. As such, we await the findings of two additional prospective randomized trials (Eastern Cooperative Oncology Group [ECOG] 2108 and Japan Clinical Oncology Group [JCOG] 1017) to help add clarity to this controversy. In ECOG 2108, patients with disease who do not progress during initial systemic therapy are randomized to continued systemic therapy versus surgery with intention for negative surgical margins, either through breast-conserving therapy (BCT) involving lumpectomy and radiation therapy or total mastectomy with or without radiation. Similarly JCOG 1017 is studying patients with stage 4 disease who receive primary systemic therapy according to their tumor subtype, followed by randomization to surgery plus systemic therapy or to systemic therapy alone. Until the results of these additional studies are finalized, patients with de novo metastatic breast cancer should not be managed with surgical intervention as a means to improve survival.

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