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Editorial

Are we close to the end of the primary tumor resection discussion for *de novo* stage IV BC?

Retrospective data showed that breast surgeons all over the world had done primary tumor surgery on patients who had *de novo* stage IV BC although there was no evidence previously. After publications with retrospective data and meta-analyses in the last decade, oncologists ask themselves: is it time to suggest primary loco-regional treatment (LRT) on this group of patients? The incidence of synchronized distant metastatic disease in newly-diagnosed BC patients is between 5 and 10% [1,2] and, as there is no cure for metastatic BC, systemic therapy (ST) is the primary treatment choice. However, more and more studies show that ST may not be the only option. The traditional goal of surgery in such cases is to palliate symptoms and improve quality of life, but diagnosing low volume metastatic BC with new imaging modalities improved patient survival for stage IV BC; recent advances in adjuvant therapies and better understanding of tumor biology encourages us to rethink treating primary tumor locally.

The meta-analysis that appears on this EJSO issue [3] *Primary Tumor resection in stage IV breast cancer: A systematic review and meta -analysis)* like several retrospective studies and previous meta-analyses, indicates that primary tumor surgery in appropriately selected *de novo* stage IV BC patients not only controls loco-regional progression, but also prolongs overall and disease-free survival [1,2,4–6]. So far there are 2 randomized studies published with two different designs; the latest one, MF07-01 Study [7], randomized patients two study arms: (a) LRT continued with ST and (b) primary ST. ST group patients received ST immediately after randomization, whereas LRT group patients received ST after surgical primary tumor resection. LRT was complete primary tumor resection, and in clinically node-negative patients, sentinel lymph node (SLN) biopsy allowed assess of axillary involvement; SLN-positive patients underwent axillary clearance. During the 40-month follow-up, 55% (176/38) and 74% (101/136) patients died in the LRT and ST groups, respectively. Hazard of death was 34% lower in the LRT group as compared to the ST group (HR: 0.66, 95% CI 0.49–0.88, $p = 0.005$). By the fifth year of follow-up, 41.6% (95% CI 32.5–50.4) of patients were alive in the LRT group and only 24.4% (95% CI 16.9–32.6) were alive in the ST group ($p = 0.005$). This is the first randomized study to show statistically significant improvement in median survival with surgery (46 vs. 37 months; HR: 0.66, $p < 0.005$) at five-year follow-up.

The second prospective study from India was designed to give ST upfront and then randomized patients to either LRT or ST if there is a regression on the primary tumor [8]. This study showed that LRT in women with *de novo* stage IV BC did not result in any OS benefit compared with no LRT (median survival was 19.2 months vs. 20.5 months [$p = 0.79$]). Their conclusion was not encouraging LRT in *de novo* stage IV BC routinely. There is some weakness of the Indian study; although 26% (n = 45) of LRT group patients and 35% (n = 62) of no-LRT group patients had Her2/neu (+), no Her2/neu (+) patients received Her2-targeted therapy in the LRT group and 15% received such therapy in the no-LRT group.

Most retrospective studies and meta-analyses state that younger patients with bone limited metastasis and ER (+) primary tumors lived longer with LRT. The MF07-01 study with unplanned subgroup analyses, patients with ER (+) or HER2/neu (−), those with solitary bone metastasis, and patients < 55 years old had a significant survival benefit with initial surgery. At five years, 51.7% of LRT group patients and 29.2% in the ST group were still alive ($p = 0.038$). Median survival was almost 10 months longer in the LRT group compared with the ST group in solitary bone only metastasis with HR 0.47. Retrospective and prospective studies have shown that patients with fewer metastases live longer. The diagnosis of solitary bone metastasis without histological confirmation is difficult and controversial but biopsy to metastatic site is not a routine clinical practice in most breast centers. Some guidelines recommend biopsy of metastatic sites at the first recurrence to determine tumor ER/PR and Her 2 status; in case of where negative ER/PR and Her 2/neu occurred in the primary tumor; treatment may change based on positive metastatic site biopsy results. Prospective trials have shown bone biopsy samples to be 98–100% concordant with imaging studies [9,10] to decrease false negatives on imaging in solitary bone metastasis, and two imaging modalities (whole body bone scintigraphy and FDG-PET/CT) can be performed to confirm diagnoses of solitary bone metastasis as suggested in the MF07-01 study.

Is there a subgroup of patients who may not get survival benefit or worsen prognosis? Like retrospective studies, MF07-01 study also showed that multiple liver and/or pulmonary metastases had a significantly worse prognosis with initial surgery; 31% of LRT group patients survived at three years compared with 67% without surgery ($p = 0.05$). Oncologists should keep in mind that primary surgery in patients with *de novo* stage IV BC with extensive visceral organ metastasis worsens OS.

While Stage IV BC patients live longer, locoregional progression happens during their treatment. Retrospective studies conclude that, in order to decrease the risk of locoregional progression, primary breast surgery should be considered in *de novo* stage IV BC. MF07-01 study had 11 times higher locoregional progression in

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the ST group (LRT % 1 vs. ST 11%; $p = 0.001$), and in the Indian study with median 23-month follow-up, 10% of patients underwent surgical primary tumor removal for palliation and LRT resulted in a significant improvement in locoregional progression-free survival compared with no-surgery patients (HR 0.16, $p = 0.0001$) [8]. While dealing with this group of patients' oncologists should be aware that LRT controls LPR in *de novo* BC stage IV patients in whom long term survival is expected.

Therefore, as concluded once again in the meta-analysis in this volume of EJSO [3], LRT should be considered in selected cases; oncologists must consider age, performance status, comorbidities, tumor type, and metastatic disease burden while discussing LRT with patients. Newley diagnosed stage IV BC deserves comprehensive discussion and the treating team should keep in their mind that survival benefit depends on resection completeness and locoregional RT.

In conclusion, it is not the end of the discussion, but we have more solid evidence that LRT has a role in *de novo* stage IV BC. Such patients should be discussed in the tumor board for the possibility of LRT to prolong the survival and for the loco-regional control which affects the quality of life of the patient.

Conflict of interest statement

No conflicts of interest to declare.

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Atilla Soran
Department of Surgical Oncology, Breast Surgery Unit, Magee-Womens Hospital of University of Pittsburgh Medical Center, Pittsburgh, PA, USA
E-mail addresses: asoran@upmc.edu, asoran65@gmail.com.

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