



# Who can get the survival benefit of primary tumor resection for *de novo* stage IV breast cancer?

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The survival benefit of primary tumor resection for patients with *de novo* stage IV breast cancer is important but remains a controversial topic. Five randomized controlled trials have confirmed survival benefits. The results of trials from India (1), a Turkish study group (2) and the ABCSG (3) have been reported. Khan *et al.* recently published the results of a randomized clinical trial (EA2108) which evaluated early local therapy for the primary site in *de novo* stage IV breast cancer with sensitivity to optimal primary systemic therapy (4).

Khan *et al.* reported that early local therapy, for treatment of the primary site, did not improve overall survival in *de novo* stage IV breast cancer patients (3-year OS rate: 67.9% with *vs.* 68.4% without local therapy;  $P=0.57$ ). These results are consistent with those of two previous trials (India and ABCSG). The Turkish trial demonstrated the possibility of a survival benefit in patients undergoing primary tumor surgery as the initial treatment. However, multivariate analysis of the results obtained in the aforementioned four trials yielded a negative result (5). This observation is different from those described in many previous retrospective reports. The main reasons for this difference are immortal biases and selective biases. We need to consider these biases when evaluating the efficacy of local treatment. It is now well established that not all *de novo* stage IV breast cancers require resection of the primary tumor. Most notably, according to the results of the Indian trial and EA2108, if the patient cannot tolerate effective systemic therapy, primary tumor resection may actually result in a poorer outcome. The results of JCOG 1017, the

most recent trial to address this clinical question, will be reported in 2023 (6). Adequate evidence of efficacy cannot be obtained by analyzing the results of the five prospective trials conducted.

However, local control of breast was improved by primary tumor surgery in all other prospective trials. Locoregional progression was less frequent in those randomly assigned to primary tumor surgery (3-year rate: 16.3% *vs.* 39.8%;  $P<0.001$ ) Breast cancer was controlled in approximately 23% of patients receiving surgery aimed at achieving local control surgically. A reliable strategy for identifying which patients with local symptoms would benefit from primary tumor resection is needed. Selection of suitable candidates for surgery allows for avoidance of local symptoms. We randomized 20% of the patients in this trial to a non-surgery group undergoing only primary surgery. Our results indicate that approximately one quarter of *de novo* stage IV breast cancer patients require primary tumor resection in order to maintain local control. We found that surgery may even significantly impair health-related quality of life. Outcomes were significantly worse at 18 months after surgery in those receiving local control therapy. The factors predicting local symptoms and the indications for local surgery merit further discussion.

One question remains. Does local therapy including primary tumor resection prolong the survival of metastatic breast cancer patients with oligometastasis (7)? Previous reports indicated a survival benefit with local therapy for patients with oligometastasis (8). Based on the results of the Turkish study, primary tumor resection may prolong

the survival of *de novo* stage IV breast cancer patients with a solitary bone metastasis (oligometastasis). Several prospective randomized trials focused on this clinical question are being planned or are already ongoing (NGR-BR002; NCT02364557, SABR-COMET3; NCT 03862911, STEREO-SEIN; NCT02089100). We anticipate obtaining evidence from the results of these trials, conducted globally, regarding the efficacy of local therapy.

We have new evidence from the results of the aforementioned four prospective studies, including EA2108, regarding the value of and indications for local therapy in patients with *de novo* stage IV breast cancer. There are, however, important differences among and problems with each of these studies. We anticipate obtaining evidence that will finally answer this clinical question from JCOG1017 and a meta-analysis of the data from all five trials. Moreover, we have now identified another clinical question. New data from upcoming prospective trials are needed to gain a full understanding of the role of local therapy.

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