



Editorial

Impact of breast surgery in de novo stage IV breast cancer

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Comment on: Fitzal F, Bjelic-Radisic V, Knauer M, *et al.* Impact of Breast Surgery in Primary Metastasized Breast Cancer: Outcomes of the Prospective Randomized Phase III ABCSG-28 POSYTYIVE Trial. *Ann Surg* 2018. [Epub ahead of print].

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The article, entitled “Impact of Breast Surgery in Primary Metastasized Breast Cancer Outcomes of the Prospective Randomized Phase III ABCSG-28 POSYTYIVE Trial”, published in the *Annals of Surgery* (1), is the third to study to prospectively evaluate the prognostic efficacy of breast surgery in patients with metastases (Table 1). This trial evaluated breast surgery for newly diagnosed *de novo* stage IV breast cancer patients with no history of systemic therapy. After providing informed consent, patients were allocated to arm A (surgery consisting of either standard breast-conserving surgery or mastectomy including axillary staging and systemic therapy) or to arm B (systemic therapy without surgery). The patients were stratified according to grading, receptor status, HER2 status, metastasis location (visceral *vs.* bone-only metastases) and planned first-line therapy. As systemic therapy, chemotherapy, anti-HER2 therapy, or anti-hormone therapy was administered according to local standards, with regimens including modern effective drugs. The primary endpoint was overall survival (OS) and the authors reported that they could not demonstrate a prognostic benefit for primary tumor resection. Additionally, they reported worsening of the outcomes of the patients with distant metastasis. The time to distant progression in the surgery arm was shorter (though not significantly) than that in the no-surgery arm (HR 0.598, 95% CI, 0.343–1.043; $P=0.0668$). These results were very similar to those of the first report on a prospective trial from India (2) but different from the results of many retrospective reports (3). In our view, the limitation of systemic therapies is one of the reasons for this

discrepancy. In the Indian trial, the patients did not receive systemic therapies according to breast cancer subtypes. Anti-HER2 targeted therapies were not used for patients with HER2-positive subtype, and very few patients with ER-positive tumors received hormone therapy. In addition, the discontinuation of effective systemic therapy after randomization might result in a poorer outcome, especially distant progression free survival, in the patients with primary tumor resection. However, the patients received modern and continuous systemic therapy in this ABCSG trial and the results were similar to those of prior trials. Given these results, it appears that stage IV breast cancer patients should not undergo primary tumor surgery.

However, there is an important problem that needs to be addressed. Statistically, the authors planned for a control arm, systemic therapy alone: median survival 24 months, experimental arm, surgery plus systemic therapy: median survival 36 months; HR of 0.666, alpha level 5%, power 80%, drop-out rate 5%, requiring 254 patients (127 in each treatment arm) to be enrolled in order to observe 192 events. However, due to poor recruitment, the study was stopped prematurely after 5 years when only 90 patients had been enrolled, 45 in each arm. The statistical power was thus very low. Moreover, the median survival of the control arm was 54.8 months, which was longer than specified in the protocol plan, such that they would have needed more patients and a longer follow-up period than in their initial plan to detect a 6-month advantage of surgery.

The MF07-01 trial from Turkey evaluated the prognostic effects of breast surgery as the primary treatment

Table 1 The prospective trials which evaluate the prognostic efficacy of primary tumor resection

Trial group	Trial number	Accrual period (situation)	N	Initial therapy
India (Tata Memorial Hospital)	NCT00193778	2005–2012 (completed)	350	Systemic
JCOG	UMIN000005586 (JCOG1017)	2011–2018 (completed)	500/410 → 570/407	Systemic
ECOG	NCT01242800 (ECOG2108)	2011–2015 (completed)	880/660 → 368/258	Systemic
Turkey	NCT00557986 (MF07-01)	2008–2012 (completed)	281	Surgery
ABCSG	NCT01015625 (ABCSG 28)	2010–2015 (early stopped)	256 → 90	Surgery

and found that breast surgery might prolong OS (4). However, it was not possible to confirm that surgery achieves an 18% improvement of the 3-year survival rate according to their preplanned analysis. On the other hand, a longer follow-up study showed statistically significant improvement in median survival (HR 0.66; 95% CI, 0.49–0.88; P=0.005) (The authors did not plan this analysis as part of their initial protocol).

We know that the most significant treatment to improve the prognosis of metastatic breast cancer patients is the effective systemic therapy. Systemically administered drugs clearly prolong survival. Local therapy, including surgery and/or radiation, is one of the choices of additional treatment. Our aim should be to indicate the most effective treatment strategies for individual cancer patients, employing drugs, surgery and radiation, alone or in various combinations. The goals for them are to prolong their survival and to control symptoms. We want to answer the questions “Who would benefit from breast surgery?” and “When should patients receive surgery?”.

The Japan Clinical Oncology Group (JCOG 1017, UMIN000005586) (5) and Eastern Clinical Oncology Group (ECOG 2108, NCT01242800) are completing the recruitment of recruiting and following patients for a prospective trial. These trials have enough patients to allow statistically meaningful analysis of their hypothesis, and patients received the modern standard systemic therapy, including molecular target therapies, available both before and after randomization. These trials will resolve current controversies and provide many eagerly awaited answers.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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