There are many retrospective reports to indicate the survival benefit of primary tumor resection for de novo stage IV breast cancer. Moreover, several comprehensive reviews have described significant differences in survival time (hazard ratio of ~0.6) (1,2). However, retrospective reports include numerous biases. Patients undergoing surgery might be in good condition for surgery, while those not receiving surgical treatment might have poor overall condition. In addition, details regarding the efficacy and the disease control rate for systemic therapy are lacking. Currently, we don’t know the most appropriate timing for surgery or patients’ status. One of the most important questions is whether the best timing for primary tumor resection is before or after primary systemic therapy. We can determine the indications of surgery according to the efficacy of systemic therapy. Moreover, we can completely remove the locally advanced primary tumor with muscle and/or skin invasion after tumor volume reduction by systemic therapy. Lane et al. reported the results of patterns of surgical care and their association with overall survival among a contemporary cohort of women with stage IV breast cancer (3). They reported that surgical resection of the primary tumor occurs in almost half of women with stage IV breast cancer alive 1 year after diagnosis. Primary tumor resection for de novo stage IV breast cancer patients, especially after systemic therapy (before systemic therapy: hazard ratio, 0.62–0.73; after systemic therapy: hazard ratio, 0.56; P<0.001), was independently associated with improved adjusted overall survival when compared to systemic therapy alone. However, there were no details about the response to primary systemic therapy. The Translational Breast Cancer Research Consortium (TBCRC) reported results of a prospective cohort study of stage IV breast cancer patients (4). There was no significant prognostic effect of primary tumor resection for responders to primary systemic therapy. We need to confirm the indications and timing of surgery by prospective randomized trials.

Five prospective randomized trials have analyzed the efficacy of primary tumor resection for stage IV breast cancer (Table 1) (5). Three have reported final results, and the others are still currently enrolling patients or following up. The first results were from the Indian trial (6). The efficacy of primary tumor resection for Stage IV breast cancer patients with sensitivity to primary systemic therapy was evaluated, and they could not indicate the prognostic efficacy of surgery. A Turkish trial (MF07-01) (7) and the ABCSG-28 (POSYTIVE trial) (8) evaluated prognostic effects of surgery as the primary treatment before systemic therapy. The Turkish trial suggested a positive effect of primary surgery; however, the POSYTIVE trial could not demonstrate an OS benefit. We cannot get the best evidence from the prospective studies so far because these trials have had limitations in the evaluations; In the Indian trial, systemic therapies were not selected according to breast cancer subtypes. Anti-HER2 molecular targeted therapies were not used for patients with HER2-positive tumors, and very few patients with ER-positive tumors received hormone administration as primary
systemic therapy. The Regatta trial for stage IV gastric cancer reported similar results. Gastrectomy followed by chemotherapy yielded no survival benefit compared with chemotherapy alone (9). The authors suggested one of the reasons was reduced compliance with chemotherapy after surgery due to adverse events like weight loss. We think the most important treatment of metastatic cancer is effective drug from these trials’ results.

Moreover, discontinuation of effective systemic chemotherapy after randomization might result in a poorer outcome in distant progression-free survival in the patients with surgery group. This result follows the pattern of previous reports. Folkman demonstrated that the primary tumor actively secretes angiostatin, which suppresses the angiogenic activity of metastatic cancer, and that resection of the primary tumor removes that suppression, and thus increases angiogenesis and growth of metastatic lesions (10). Fisher demonstrated that animals with metastatic disease were immunologically compromised, and that surgical stress releases growth factors, which in turn stimulate proliferation of metastasized cancer cells (11). The POSYTIVE trial reported similar results; however, there were no details about systemic therapy after randomization. More data on systemic treatment are needed to evaluate this clinical question. From the results of these prospective studies, primary tumor resection for de novo stage IV breast cancer cannot be recommended to all patients routinely. The impact of surgery on survival is not so large for de novo stage IV breast cancer. We need to consider eligibility for surgery and planning integrated treatment strategies, including local therapy, according to breast cancer subtype, metastases and the patient’s condition. Our aim should be to devise the most effective treatment strategies for individual cancer patients, employing drugs, surgery and radiation, alone or in combination. The treatment goals for stage IV breast cancer are to prolong the patient’s survival time and to control symptoms.

The Japan Clinical Oncology Group (JCOG 1017) and Eastern Clinical Oncology Group (ECOG 2108) are enrolling and following patients for a phase 3 trial (Figure 1). In these trials, patients received the most up-to-date standard systemic therapy available before and after randomization, and also the most advanced form of imaging examination available before treatment. It is anticipated that the aforementioned trials will resolve current controversies and provide many eagerly awaited answers.

### Table 1 Randomized clinical trials

<table>
<thead>
<tr>
<th>Country (trial group)</th>
<th>Trial number</th>
<th>Accrual period (situation)</th>
<th>N</th>
<th>Initial therapy</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>NCT00193778</td>
<td>2005–2012 (completed)</td>
<td>350</td>
<td>Systemic therapy</td>
<td>Overall survival</td>
</tr>
<tr>
<td>Japan (JCOG)</td>
<td>UMIN000005586 (JCOG1017)</td>
<td>2011–May 2018 (completed)</td>
<td>500/410→600/410</td>
<td>Systemic therapy</td>
<td>Overall survival</td>
</tr>
<tr>
<td>USA and Canada (ECOG)</td>
<td>NCT01242800 (ECOG2108)</td>
<td>2011–2015 (completed)</td>
<td>880/660→368/258</td>
<td>Systemic therapy</td>
<td>Overall survival</td>
</tr>
<tr>
<td>Turkey</td>
<td>NCT00557986 (MF07-01)</td>
<td>2008–2012 (completed)</td>
<td>281</td>
<td>Surgery</td>
<td>Overall survival</td>
</tr>
<tr>
<td>Austria (ABCSG)</td>
<td>NCT01015625 (ABCSG 28)</td>
<td>2010–2015 (early stopped)</td>
<td>256→90</td>
<td>Surgery</td>
<td>Overall survival</td>
</tr>
</tbody>
</table>
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Footnote

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