Surgery of the primary tumor in \textit{de novo} metastatic breast cancer: To do or not to do?

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Abstract

Approximately five percent of all breast cancer patients in developed countries present with distant metastases at initial diagnosis. Due to its incurability, metastatic breast cancer is generally treated with systemic therapies to achieve disease control and reduce tumor-related symptoms. Primary treatments for metastatic breast cancer are chemotherapy, endocrine- and biologic therapy, whereas surgery with or without radiotherapy is usually performed to treat impending wound issues. Since 2002, several retrospective non-randomized clinical studies have shown that excision of the primary tumor correlates with a significantly improved survival in patients with primary metastatic breast cancer. Others have argued that this survival benefit associated with surgery may be due to selection biases. Therefore, in the absence of published results from randomized controlled trials carried out in India and Turkey and completion of a trial in the United States, there is no clear conclusion on whether surgical excision of the primary breast cancer translates into a survival benefit for patients with \textit{de novo} metastatic disease. Furthermore, timing and type of surgical procedure, as well as selection of patients who could benefit the most from this approach, represent additional points of uncertainty. Despite the epidemiological burden of this condition, there are no guidelines on how to manage breast cancer patients presenting with \textit{de novo} metastatic breast cancer; and decisions are often left to provider and patient preferences. Here, we present a critical overview of the literature focusing on the rationale and potential role of primary tumor excision in patients with \textit{de novo} metastatic breast cancer.

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Introduction

Despite the remarkable progress achieved in breast cancer screening and early diagnosis over the past three decades, approximately five percent of all breast cancer patients in United States and Western Europe have distant metastases at initial presentation.\textsuperscript{1–3} Up to 50% — from a surgical viewpoint — have locally-resectable primary breast tumors.\textsuperscript{4} Traditionally, these patients are principally treated with systemic approaches, as metastatic breast cancer is considered to be an incurable, although treatable disease. In this setting, primary treatment aims at improving both
duration and quality of life. Local therapy has traditionally been reserved for metastatic patients, in whom the breast tumor is symptomatic (i.e. the so-called “toilette mastectomy”). The justification for this strategy of limited surgical therapy is based on the fact that once distant metastases have occurred; local therapies are thought to provide no survival advantage. However, in the era of personalized medicine, multidisciplinary and targeted treatment approaches may be required in order to tackle the clinical and biological heterogeneity of metastatic breast cancer, fulfill individual patient preferences and potentially improve overall survival with the use of local therapy. We have to consider that the improved overall survival achieved with the new therapeutic modalities requires us to revisit the role of local therapy in this group. Furthermore, the biological rationale for removing the primary tumor in de novo metastatic breast cancer has been debated for years. On one hand, removal of the primary tumor is thought to be positive, as it is supposed to reduce the overall tumor burden and source of metastatic spread. Indeed, primary breast tumor may represent itself a continuous source of cells that acquired metastatic competence and thus can be responsible for metastatic dissemination. Moreover, according to preclinical evidence supporting the hypothesis of “cancer self-seeding”, tumor cells may be able to recirculate from metastatic sites to their original site of production, favoring both systemic and locoregional disease progression. In addition, surgery may restore immunocompetence, as the primary tumor modulates anti-cancer immune responses by releasing immunosuppressive factors. Finally, systemic therapy may be more effective in presence of reduced tumor burden by decreasing the emergence of chemo-resistant clones and removing necrotic tumor tissue scantily accessible to drugs. The other school of thought suggests that, the primary tumor can represent a source of antiangiogenic factors and growth factor inhibitors, suggesting that its removal may lead to an accelerated relapse. Other potential drawbacks might be also related to the release of growth factors associated with surgical wounding and with the immunosuppression induced by both surgery and anesthesia. Also the clinical sequelae from surgical removal of primary tumor, such as the morbidity and risks associated with the procedure itself, postsurgical morbidity (i.e. lymphedema, flap necrosis), and delayed administration of systemic therapy. Therefore, considering these opposing hypotheses and the lack of published results from prospective randomized clinical trials, the role of breast surgery in the management of de novo metastatic breast cancer remains unclear.

Below we present a critical overview of the major retrospective studies assessing the effect of primary tumour excision on the outcome of patients with de novo metastatic breast cancer. Furthermore, we discuss about the timing and type of surgical procedure, as well as the value that surgery may have in metastatic patients in different clinical scenarios.

Review

Research on the effect of systemic therapy in women with metastatic disease has demonstrated that their prognosis has significantly improved over the past 10—15 years, primarily due to increased efficacy of chemotherapy, endocrine therapy, as well as to the introduction of targeted treatments.

In 2002, Seema Khan presented at the Central Surgical Society meeting in the United States data from the National Cancer Data Bank of the American College of Surgeons on the purported survival benefit of local therapy in the stage IV setting. The subsequent publication in Surgery led to a flurry of retrospective studies have shown that also surgical removal of the breast primary tumor could be significantly associated with improved prognosis in patients with de novo metastatic breast cancer. These studies based on either single institution data or population datasets, reported hazard ratios (HR) for overall survival (OS) ranging between 0.50 and 0.8 in favor of surgical removal of the primary tumor (Table 1). In several cases, these survival differences were not statistically significant probably due to small sample size. Ruijterkamp et al. calculated a pooled OS HR of 0.65 in favor of surgery versus no surgery. Besides the general effect of primary tumor excision, some studies evaluated also the specific impact on patient outcome of surgical resection margins, showing better survival in patients with free surgical margins after primary breast tumor removal. Moreover, the extent and site of metastatic disease may influence the effect of surgery, as suggested in a study where a greater effect on survival was observed among women undergoing surgery with bone only metastases at diagnosis.

However, in the above mentioned studies, favorable prognostic factors or selection bias, such as younger age, better performance status, smaller size of primary tumor, limited metastatic dissemination, and good response to prior systemic therapy may have influenced the decision to perform surgery and possibly limiting the scientific value and reliability of the retrospective studies. In order to limit the impact of potential confounders, in most studies the effect of surgery on survival was adjusted for common prognostic factors in metastatic breast cancer, such as age, tumor size, number and sites of metastases, and disease biology. Additionally, in some studies the analysis was also adjusted for comorbidity or status of surgical margins.

The group at the Harvard Hospitals was the first to suggest that surgical extirpation of the primary tumor might not be of benefit. The role of additional confounding factors, such as timing of surgery, type of systemic treatment administered prior to surgery, and coding errors were investigated, thus suggesting that the survival benefit seen in patients who underwent surgical resection of the primary tumor may not be present or may have been merely related to the presence of these confounders. For instance, in one study, the benefit of surgery seemed to be restricted to
patients who underwent surgery before diagnosis of metastatic disease, whereas no survival advantage was observed in patients who underwent surgery of the breast tumor after the metastatic disease was diagnosed, an example of stage migration. In another study, the surgery benefit appeared in the multivariate analysis when adjusting for administration of chemotherapy. Interestingly, coding errors in retrospectively collected data were found to partly explain the survival advantage in one of the reported studies. Despite these contradictory results, a meta-analysis of 15 studies reported that surgery of the primary tumor was independently associated with improved survival in the multivariate analyses. However, as all the included studies were retrospective, and based on this, one cannot conclude that surgical removal of the primary breast tumor improves overall survival. Therefore, several randomized controlled trials were designed to determine if local therapy would improve survival in a randomized fashion in patients with metastatic breast cancer. In our opinion, multimodal treatments must be discussed based on a multidisciplinary approaches (systemic therapy, surgery and radiotherapy), performed with curative intent. In our opinion, multimodal treatments must be discussed and evaluated in the vast majority of cases of metastatic breast cancer, however we would only recommend local therapy in selected cases where clinically feasible.

Ongoing randomized prospective trial ECOG 2018 and the publication of the two completed trials will hopefully help determine whether a subset of patients with stage IV disease will benefit from local therapy. There is likely a subset of patients who will benefit the most from breast surgery, rather than defining the role of such approach to the general population of patients with metastatic breast cancer. In this regard, it has been hypothesized that oligometastatic breast cancer represents an intermediate stage of metastatic disease associated with an indolent disease course and prolonged survival, mainly in patients receiving multidisciplinary treatment approaches. Basing on this hypothesis and on the evidence from the Turkish Federation of Societies for Breast Diseases Soran et al., suggested that patients with isolated bone metastases may benefit from surgery, whereas such an approach was even detrimental in patients with visceral involvement. The results suggest surgery was not of benefit in the majority of patients, and in fact may lead to worse outcome as reported in the TATA study. A subgroup with isolated or bone only metastasis may benefit from surgical excision of breast primary tumor, confirming the observations of the retrospective series from British Columbia, one of the published population-based analyses mentioned above.

### Discussion

The treatment of metastatic breast cancer is complex and one must consider multiple factors, such as tumor biology, burden, patient specific factors and heterogeneity in the tailoring of patient centered care. Traditionally, the principle of incurability of metastatic disease has deeply influenced clinical research in metastatic breast cancer, resulting in the lack of high-level evidence supporting multi-modality based on a multidisciplinary approaches (systemic therapy, surgery and radiotherapy), performed with curative intent. In our opinion, multimodal treatments must be discussed and evaluated in the vast majority of cases of metastatic breast cancer, however we would only recommend local therapy in selected cases where clinically feasible.

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### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Data source</th>
<th>No. of pts (% of pts receiving surgery)</th>
<th>Median OS (mo)</th>
<th>OS HR (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khan et al. 2002</td>
<td>Population</td>
<td>16,023 (57)</td>
<td>31.9 vs 19</td>
<td>0.61 (0.58–0.65)</td>
</tr>
<tr>
<td>Rapiti et al. 2006</td>
<td>Population</td>
<td>300 (42)</td>
<td>NA</td>
<td>0.6 (0.4–1.0)</td>
</tr>
<tr>
<td>Gnerlich et al. 2007</td>
<td>Population</td>
<td>9734 (47)</td>
<td>36 vs 21</td>
<td>0.63 (0.6–0.66)</td>
</tr>
<tr>
<td>Fields et al. 2007</td>
<td>Single institution</td>
<td>409 (46)</td>
<td>31.9 vs 15.4</td>
<td>0.53 (0.42–0.67)</td>
</tr>
<tr>
<td>Blanchard et al. 2008</td>
<td>Population</td>
<td>395 (61)</td>
<td>27.1 vs 16.8</td>
<td>0.71 (0.56–0.91)</td>
</tr>
<tr>
<td>Cady et al. 2008</td>
<td>Two institutions</td>
<td>622 (38)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rao et al. 2008</td>
<td>Single institution</td>
<td>82 (100)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hazard et al. 2008</td>
<td>Single institution</td>
<td>111 (42)</td>
<td>26.3 vs 29.2</td>
<td>0.798 (0.4–1.52)</td>
</tr>
<tr>
<td>Ruiterkamp et al. 2009</td>
<td>Population</td>
<td>728 (40)</td>
<td>31 vs 14</td>
<td>0.62 (0.51–0.76)</td>
</tr>
<tr>
<td>Baffle et al. 2009</td>
<td>Three institutions</td>
<td>147 (41)</td>
<td>42.2 vs 28.3</td>
<td>0.47 (NA)</td>
</tr>
<tr>
<td>Neum et al. 2010</td>
<td>Single institution</td>
<td>186 (37)</td>
<td>40 vs 33</td>
<td>0.71 (0.47–1.06)</td>
</tr>
<tr>
<td>Leung et al. 2010</td>
<td>Single institution</td>
<td>157 (33)</td>
<td>25 vs 13</td>
<td>NA</td>
</tr>
<tr>
<td>Dominici et al. 2011</td>
<td>Population</td>
<td>290 (19)</td>
<td>42 vs 41</td>
<td>0.94 (0.83–1.08)</td>
</tr>
<tr>
<td>Nguyen et al. 2012</td>
<td>Population</td>
<td>733 (40)</td>
<td>NA</td>
<td>0.78 (0.64–0.94)</td>
</tr>
<tr>
<td>Lang et al. 2013</td>
<td>Single institution</td>
<td>208 (36)</td>
<td>56.1 vs 37.2</td>
<td>0.58 (0.35–0.98)</td>
</tr>
</tbody>
</table>
tumor cells (CTCs) may allow to identify metastatic breast cancer patients who have lower probability to suffer from further metastatic dissemination and thus higher chances to benefit from loco-regional ablative procedures, administered with a curative intent.40 Future prospective studies will be designed to address these issues.

Additional open questions concern the ideal timing of surgery and the type of surgical procedure. Interestingly, Bafford et al. found in their retrospective analysis that survival benefit from breast surgery was limited to patients undergoing surgery before diagnosis of metastatic disease when the patient was not deemed metastatic and surgery was felt to have been performed for curative intent.30 The authors concluded that this observation was likely a consequence of stage migration bias.30 In contrast, Rao et al. showed that survival benefit was only present when surgery was performed more than 3 months after diagnosis.28 In the absence of studies designed to address this specific issue, and considering that primary systemic treatment remains the standard approach for metastatic breast cancer patients, we can presume that performing breast surgery in metastatic patients outside clinical trials might be considered a clinically reasonable approach only in patients with limited metastatic burden and who have achieved a good and long-lasting control of disease for nearly six months after initial systemic therapy. In terms of the surgical procedure, some of the retrospective studies presented in this review showed that patients with free surgical margins after primary breast tumor removal had better outcome.7,20,28 This may suggest the importance to perform surgery, as one would in the non-metastatic setting with appropriate lymph node evaluation, margin definition and use of radiotherapy. The value of axillary dissection in this subset of patients needs to be prospectively addressed, as information on the use of this procedure in this population is scant. Another important and unaddressed point concerns the optimal integration between surgery and systemic therapy. So far, it is still unclear if the removal of the breast primary is advisable soon after the response to systemic therapy or at a later stage or, provocatively speaking, as the first step in the therapeutic path, when the patient has not experienced the side effects of systemic therapy yet.

In conclusion, it is still unknown how to properly select metastatic patients who could benefit from breast surgery, as well as which is the optimal timing and type of surgical procedure to be adopted in these selected patients. The relatively low morbidity associated with breast surgery makes this an ideal model for a prospective investigation on the surgical excision of the primary in patients with metastatic disease. It is worth highlighting here that breast surgery in the context of advanced disease needs to be as safe as possible, in order to avoid delays in the subsequent systemic therapy.

More conclusive data will hopefully come from the publication and completion of randomized controlled trials. At this time the role of local therapy should be reserved for palliation and consideration of those with low burden oligometastatic disease who have responded to initial systemic therapy. If surgery is to be done it should mirror those in the non-metastatic setting.

Competing interests
The authors declare that they have no competing interests.

References