

Controversies in Surgery of the Primary Tumor in Metastatic Breast Cancer

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Abstract

Metastatic breast cancer (stage IV) is classified either as *de novo* disease or as metachronous disease. For the *de novo* appearance (so-called naïve), the current best practice is systemic therapy; the role of primary surgery is still a matter of debate. Several retrospective and clinical trials have been reported which aimed to assess the impact on survival of primary surgery in women with metastatic breast cancer. In this critical review, we revised these results, reporting data on the latest clinical trials and we offer some suggestions for the surgical management of stage IV breast cancer.

Keywords: Breast cancer; Primary surgery; Tumor metastasis

Introduction

Metastatic Breast Cancer (MBC) is currently a clinical burden due to the difficulty in choosing treatment options. This aggressive disease (defined as stage IV) represents about of 4-5% of all cases in United States and Europe [1,2]. In developing countries, we have observed an increased rate of MBC, ranging from 10% to 44% in Malaysia and Nigeria respectively [3,4]. MBC is classified as a *de novo* disease, as first manifestation, or metachronous stage IV, whenever the diagnosis is performed following an initial localized BC with an interval of disease free-survival. Clinical evidence demonstrates that in both situations MBC is an inexorable disease; often, palliative treatments are the only option to prevent or reduce symptomatology. However, with the advent of the so-called targeted therapies, palliative treatments are being progressively replaced by systemic therapy, aiming to convert the metastatic cancer into a chronic disease. In fact, it has been verified that patients with MBC have begun to demonstrate a slight improvement in survival [5]. If systemic therapies exert an unquestionable role, primary surgery is not universally considered in the treatment of MBC. Several criticisms indicate that primary surgery is an absolute contraindication, but with a careful consideration other studies are cautiously suggestive of a surgical approach even for stage IV.

Contraindications for Primary Breast Surgery

Primary surgery is generally considered a contraindication for metastatic cancers, due to the absence of any survival benefit, and the increased risk of postoperative adverse events. As in standard BC treatment, there is the risk of hematoma, infection, lymphorrhea and delay in healing, in particular if combined with axillary dissection or breast reconstruction. However, the most important question regarding primary surgery for MBC is the delay in systemic treatment, which is frequently the sole lifesaving approach for these patients. It has been demonstrated in fact that delays in systemic treatment can negatively impact survival, in particular if chemotherapy is initiated more than 12 weeks after surgery in cases of early-stage BC. This evidence is even more compelling in MBC [6].

Interestingly enough, another argument against primary surgery in this situation is the “preservation” of primary BC, to observe whenever possible the progressive clinical down staging and the response of systemic treatment.

In vitro studies demonstrated that primary surgical excision had a promoting effect on tumor growth and pulmonary metastasis of human breast cells, because the surgical procedure could also increase the vascular endothelial growth factor expression in tumor tissues [7].

Indications for Primary Breast Surgery

Cancer metastasis is a complex disease; novel theories debate the new so-called “homing phenomenon”. Clinical evidence suggests that a homing mechanism is responsible for some unlikely metastatic deposits. For example, BC often disseminates first to the bone and/or liver. The homing phenomenon may be related to the tumor cell recognition of specific “exit sites” from the circulation or to the awareness of a particularly favorable or forbidding “soil” of another tissue. This may occur because of an affinity that exists between receptor proteins on the surface of cancer cells and molecules that are abundant in specific tissues. The theory is that primary surgical excision could reduce the homing phenomenon. The first argument in favor of primary surgery in MBC treatment is that survival and outcome present a challenge. To date, there are several studies that report better survival in MBC. It seems that “recent” patients with MBC, show an improved survival compared with those treated in the past.

A single-study demonstrated that patients with MBC treated during the years 1974-1979 presented a shortened survival (median of 15 months), compared with women treated during 1995-2000 (median 58 months) [8]. Andre, et al. [5] described how temporal trends in survival were improved for MBC patients when compared the intervals 1994-2000 and 1987-1993. Interestingly, Dawood, et al. [9] verified the outcomes between patients with *de novo* stage IV BC and those with metachronous metastasis (during follow up time). Patients with *de novo* metastasis presented a longer median survival, and patients with metachronous metastasis showed worse outcomes. The reason for these differences is related to chemosensitivity, which is greater in untreated patients. Individuals previously treated could develop a mechanism of chemoresistance [10]. The second argument in favor of primary surgery in MBC is the concept of so-called “cytoreductive surgery”. The aim of cytoreductive surgery is to achieve as much debulking of the volume of the tumor as possible, rendering therapies more effective. In several primary epithelial cancers, cytoreductive surgery is performed, but has not yet been conducted in MBC. The removal or reduction of the primary tumor could theoretically reduce either self-seeding, tumor cell dissemination, or the native cancer stem cells. However, in other laboratory studies, primary tumor excision could accelerate the growth of metastasis, and it is preferable to consider theoretically a first approach with systemic therapies [11].

Retrospective Studies

There are several retrospective studies examining the outcome of surgical resection of primary BC. Petrelli & Barni [12] reported a large metanalysis including 15 retrospective studies. Results demonstrated that primary surgery was independently associated with longer survival, reducing the risk of death by 30%, in particular when it was associated with other systemic and/or local

treatments. A second significant metanalysis by Headon, et al. [13], examined 16 studies with 15,368 stage IV operated BC patients vs. 14,313 non-operated patients. Results showed a significant reduction of mortality in patients who underwent surgical resection of the primary tumor. Unfortunately, these multiple retrospective studies suffered from selection bias; recently the Surveillance, Epidemiology, and End Results (SEER) program conducted a propensity-matched analysis using 18 databases, aiming to study the impact of primary tumor resection on survival in stage IV BC [14]. For this analysis, 29,916 patients were enrolled who had been diagnosed with MBC between 1988 and 2011. About 50% of these patients underwent primary tumor resection. The study also showed an increased trend of MBC from 2% in 1998 to 8% in last decade, and the rate of operated patients with MBC decreased from 62% in 1988-1998 to 46% in 1999-2011.

A univariate analysis of patients who underwent primary tumor resection showed a greater disease-specific survival (34 vs. 18 months, $p<0.0001$). Moreover, multivariate analysis verified that not undergoing primary tumor resection was independently associated with increased mortality ($p<0.0001$). In multivariate analysis, surgery in earlier years was associated with increased mortality ($p<0.0001$). A Cox proportional hazard regression analysis was carried out matching surgery vs. no surgery. This process confirmed that primary tumor resection in IV stage BC was associated with a survival advantage: median survival was 19 months for no surgery and 34 months for surgery ($p<0.0001$). This study finally suggested a multidisciplinary discussion of patients with MBC. Some benefits can be obtained from primary surgery, in particular in oligometastatic disease (for naïve presentation) and in long-term stable disease (for metachronous manifestation).

Clinical Trial Studies

There are several clinical trials reported in the literature; we have selected four consistent studies. Two trials were conducted after systemic treatments (NCT00193778, JCOG1017) and two trials before systemic treatments (NCT00557986, NCT01392586). NCT00193778 was an open-label, randomized, controlled trial, in which previously untreated patients were recruited from Tata Memorial Centre, Mumbai, India, who had age at onset ≤ 65 years, and presented with *de-novo* MBC. These patients were randomly assigned (1:1) for Loco-Regional Treatment (LRT) directed at their primary breast tumor and axillary lymph nodes, or no locoregional care. A total of 350 BC patients were enrolled for this randomization (eligible 300 individuals: 173 to LRT and 177 to non-LRT). Median overall survival was 19.2 months (95% CI 15.98-22.46) in the LRT group and 20.5 months (16.96-23.98) in the non-LRT group (HR 1.04, 95% CI 0.81-1.34; $p=0.79$). The major finding of this randomization was that there was no evidence that LRT of the primary tumor resulted in improvement of overall survival in patients with MBC, in particular at initial presentation

that responded to front-line chemotherapy [15].

The Japanese trial JCOG1017 took into consideration patients receiving primary systemic therapy according to biological features. After 3 months, the patients without disease progression were randomized to the primary tumor resection plus systemic therapy arm, or to the systemic therapy alone arm. This study started in May 2011 with 410 patients (5 years of recruitment), aiming to assess the overall survival and other factors [16]. The latest trial was performed by the Turkish Federation of Breast Diseases (NCT00557986) [17]. The MF07-01 trial was a multicenter, phase III, randomized, controlled study comparing LRT followed by Systemic Therapy (ST) with ST alone for treatment-naïve stage IV BC patients. BC patients were randomized 1:1 to either the LRT or ST group. The trial enrolled 274 patients: 138 in the LRT group and 136 in the ST group. Risk of death was statistically lower in the LRT group than in the ST group with respect to ER and PgR status (positive) ($p=0.01$), HER2 (negative) ($p=0.01$), age at onset <55 years ($p=0.007$), and patients with solitary bone-only metastases ($p=0.04$). The study confirmed only that a longer follow-up study (median of 40 months) showed statistically significant improvement in median survival. The NCT01392586 trial in the Netherlands was closed after enrollment of 10 patients [18].

Prospective Studies

The Translational Breast Cancer Research Consortium (TBCRC) 013 was a multicenter prospective registry study with the primary goal of evaluating the role of surgery of the primary tumor in patients with stage IV BC. In this study the 21-gene Recurrence Score (RS) was evaluated [19]. A total of 127 patients from 14 sites were enrolled in this study. Of these, 109 patients were eligible for 21-gene RS analysis. RS was classified as low risk (23%), intermediate risk (28%), and high risk (49%). In all cases, RS was associated with time to first progression ($p=.01$) and 2-year overall survival ($p=.04$). In multivariable Cox regression models among patients with ER+/HER2 negative tumor, RS was independently prognostic for time to first progression ($p=.02$) and 2-year overall survival ($p=.013$). Interestingly, these results verified that the 21-gene RS was independently prognostic for both time to first progression and 2-year overall survival in ER+/HER2 negative *de novo* stage IV BC.

Conclusions

Stage IV BC is a chronic and inexorable disease; the only goals of treatment are prolongation of life and palliation or prevention of symptoms. Retrospective studies and the latest clinical trial (NCT00557986) [17] suggest that LRT for the primary tumor may provide a survival advantage in women with MBC. Conversely, other trials have demonstrated that primary surgery does not provide any advantage in survival. These contrasting results could be due to the presence of biases in both retrospective and trials studies.

However, considering the above-mentioned studies, we can accept with reservations that LRT for primary tumor could be offered to patients with the following characteristics: a) good performance status, b) smaller primary tumor, c) positive ER/ PgR expression and HER2 negative, d) oligometastatic manifestation. In the case of breast-conserving surgery, whenever surgical margins are not clear, re-excision for involvement of the resection margins should be avoided. Regarding mastectomy, breast reconstruction is not absolutely contraindicated, but must be evaluated carefully on a case-by-case basis. In the case of axillary surgery, sentinel lymph-node biopsy and axillary dissection are contraindicated, because this approach is unnecessary for prognostic information. However, for local control of the disease, it could be considered only removal of macroscopic and symptomatic axillary disease.

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