



De novo Stage IV Luminal Breast Cancer: Yes or No for Local Treatment? Serial Cases and Review

Marija Karakolevska-Ilova^{1*}, Elena Simeonovska-Joveva², Aleksandar Serafimov³

¹Department of Oncology, Faculty of Medical Sciences, University Goce Delchev Shtip, Clinical Hospital Shtip, Shtip, Macedonia; ²Department of Neurology, Faculty of Medical Sciences, University Goce Delchev Shtip, Clinical Hospital Shtip, Shtip, Macedonia; ³Department of Cardiology, Faculty of Medical Sciences, University Goce Delchev Shtip, Clinical Hospital Shtip, Shtip, Macedonia

Abstract

BACKGROUND: Primary stage IV breast cancer accounts about of 3–5% of newly diagnosed breast cancer cases. The management of this patient subset mostly comprises systemic therapy, with additional surgery or radiotherapy to control locoregional symptoms. Some of the retrospective studies showed the benefit of locoregional treatment as the first treatment of choice for overall survival (OS), but the efficacy of primary site surgery remains controversial for OS in prospective, controlled trials.

AIM: We aimed to presents series of cases with primary metastatic breast cancer with diffuse bone metastasis.

MATERIALS AND METHODS: This study was serial of cases with primary metastatic breast cancer with diffuse bone metastasis and a review of the literature. All of the cases were treated with upfront surgical resection of the primary in the breast.

RESULTS: During the follow-up period of 36 months, all of our patients were still alive.

CONCLUSION: Retrospective studies about resection of primary tumor as the first treatment of choice are with conflicting results, which may be related to randomization bias, including different biological types of breast cancer, different metastatic sites, and patients with different menopausal status. On the other hand, prospective studies did not show any powerful results that would lead the treatment in de novo stage IV breast cancer because of few limitations such a short follow-up period (between 23 and 40 months), younger patients, ER-positive/HER2 negative tumors, and type of chemotherapy given or not upfront. The effect of upfront surgery in newly metastatic breast cancer patients is still challenging, so there is a need to identify the exact cohort of patients who could benefit from surgery.

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***Correspondence:** Marija Karakolevska-Ilova, Department of Oncology, Faculty of Medical Sciences, University Goce Delchev Shtip, Clinical Hospital Shtip, Shtip, Macedonia. E-mail: marija.karakolevska@ugd.edu.mk
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Introduction

Primary metastatic stage IV breast cancer is a relatively rare disease. About 3–5% of newly diagnosed breast cancer cases are stage IV disease with synchronous metastasis. Metastatic breast cancer is not a curable disease, but according to the development of new therapies, there is an evident prolongation of survival in these patients group. The management of this patient subset mostly comprises systemic therapy, with additional surgery or radiotherapy to control locoregional symptoms and eventually the possibility of increasing the effectiveness of chemotherapy. On the other hand, local treatments may lead to reducing the total tumor burden, restore immunity, eliminate breast cancer stem cells, and decrease the likelihood of resistant disease, which may lower the metastatic potential of the primary tumor.

Most patients with *de novo* stage IV breast cancer were treated with systemic therapy only because the efficacy of local treatment, such as surgery and/

or radiotherapy, remains controversial and there are still significant differences in the distribution regarding local treatment strategies in these patients. When local treatment is an option, all the factors should be included: Age, performance status, comorbidities, tumor type, and metastatic disease burden.

There are still controversies about the type of local treatment: Surgery and/or radiotherapy, or no local treatment at all. The prospective randomized phase III ABCSG-28 POSYITIVE trial (from 2011 until 2015) evaluated median survival comparing primary surgery followed by systemic therapy to primary systemic therapy in *de novo* stage IV breast cancer and could not demonstrate an overall survival (OS) benefit for surgical resection of the primary in breast cancer patients presenting with *de novo* stage IV disease [1].

Surgery for primary metastatic breast cancer was used only for palliation purposes [2]. This approach was demonstrated by many retrospective trials [3], [4], but we still need randomized trials because until now they showed conflict results in favor of primary local therapy or primary systemic therapy.

Materials and Methods

This study was a serial of cases. We evaluated the outcome of three patients from their first visit at our clinic (July 2018) until July 2021. The patients were with primary metastatic breast cancer with bone metastases at first presentation.

First case: Woman, 42 years old, premenopausal, unmarried, without comorbidities with locally advanced breast cancer with generalized bone metastases (osteolytic metastases to ribs, cervical and thoracic spine, sternum, and both hips) on bone scan, without visceral metastasis on whole-body computed tomography (CT) scan. The first treatment of choice for this patient was local treatment: Resection of the primary in the breast (total mastectomy and axillary lymph node dissection). According to pathological and IHH findings from surgical specimen: ductal carcinoma, T2 (3 sm) N1M1, G2, R0L0V0, luminal A type, the patient was set on systemic therapy with hormone therapy (dual blockade with Tamoxifen and GnRH antagonist) and bisphosphonates.

Second case: Woman, 62 years old, postmenopausal, married, mother of two, without comorbidities with advanced breast cancer with generalized bone metastases (to cervical and thoracic spine and right 6th rib and left 9th rib) without any visceral spread. Local treatment with resection of the primary in the breast was first treatment of choice (total mastectomy and axillary lymph node dissection). According to pathological and IHH findings from surgical specimen: Ductal carcinoma, T2 (4 sm) N2M1, G2, R0L1V0, luminal A type, the patient was set on systemic therapy with hormone therapy/aromatase inhibitor and bisphosphonates.

Third case: Woman, 72 years old, postmenopausal, married, mother of two, without comorbidities with locally advanced breast cancer with generalized bone metastases (osteolytic metastases through whole spine and to both hips). Whole-body CT scan showed metastatic spread to lungs (one solitary metastasis to right lung). The first treatment of choice was the surgery of the breast and removal of lung metastasis. According to pathological findings: ductal carcinoma, T2 (2,5sm) N1M1, G2, R0L0V0, luminal A type, the patient was set on systemic therapy with hormone therapy / aromatase inhibitor and bisphosphonates.

Results

All three patients were follow-up for 36 months according to the protocol (ultrasound of breast and axilla every 6 months with mammography annually, whole

blood examination with breast cancer-related tumor markers every 6 months and abdominal ultrasound every 6 months). All three patients remain alive during follow-up period.

Discussion

Metastatic breast cancer is a disease with a median OS of 3-year and with 5-year survival rate of only 25% [5]. OS rate has improved over the years based on the progress of treatment options, which could improve quality of life, reduce tumor burden, and related complications and symptoms.

Conflicting evidence exists regarding the value of surgical resection of the primary in stage IV breast cancer patients [6], [7].

There are many retrospective studies about resection of primary tumor as the first treatment of choice, but they are with conflicting results, which may be related to randomization bias, including different biological types of breast cancer, different metastatic sites, and patients with different menopausal status [8], [9]. Recent retrospective trials have shown a positive impact of local treatment for OS and disease control in primary metastatic breast cancer after primary site tumor resection [10], [11], [12].

A retrospective study of 16023 patients from 1990 to 1993 evaluated the impact of primary local therapy with surgery for OS of *de novo* stage IV breast cancer. In a multivariate analysis, the number of metastatic sites, the type of metastatic burden, and the extent of resection of the primary tumor were identified as significant independent prognostic covariates. Women treated with surgical resection with free margins, when compared with those not surgically treated, had a superior prognosis, namely the risk of death was reduced by 39% in patients with negative surgical margins, and the 3-year survival rate was 35% compared with 17.3% in the non-operative group [13].

A more aggressive treatment approach may be appropriate for those patients in whom metastatic disease is limited to a solitary lesion or to multiple lesions at a single organ site. When those patients with local treatment (surgery or radiation) became free of local disease, there might be the potential of achieving a complete remission from chemotherapy, and patients might remain disease-free for prolonged periods of time (15–20 years or more).

A retrospective, population-based cohort study using the 1988–2003 surveillance, epidemiology, and end results program data for 9734 patients with primary metastatic breast cancer after controlling for potential confounding demographic, tumor, and treatment-related

variables showed that patients who underwent surgery were less likely to die during the study period (OS of 36 months) compared with women who did not undergo surgery (OS of 21 months) [14]. In the study of Singletary *et al.*, available literature from 1992 to 2002 was assessed to determine the role of surgery on survival outcomes and to determine appropriate criteria for selecting the best candidates for surgery and showed that primer surgery could benefit for OS [15].

Several kinds of bias might influence these results, so the data are suggestive and support the need for well-designed clinical trials to determine the exact role of surgical intervention in patients with metastatic breast cancer.

Another population-based retrospective cohort study including 987 patients with primary stage IV breast cancer, stratified according to hormone receptors, HER2 expression, age, and site of metastatic disease was conducted in China between January 2004 and December 2018 and showed that patients who underwent surgery were 54% less likely to die during the study period than patients who did not. Even among patients who died during follow-up, patients who underwent surgery on their primary breast tumor had longer median survival than those who did not (21.5 vs. 14.0 months $p < 0.001$) [16].

On the other hand, the study from 2009, which evaluated patients (147) from 1998 until 2005, in a multivariate analysis showed significantly superior survival in the surgery group (HR: 0.47, $p = 0.003$ mean 4.13 years vs. 2.36 years) compared to non-surgery group. ER and HER2 status were positive predictors of survival ($p < 0.0001$). Central nervous system and liver metastases were adverse predictors ($p = 0.059$). The study showed that benefit was only for patients treated with surgery before diagnosis of metastatic disease and was likely a consequence of stage migration bias [9].

In the retrospective study of Dominici *et al.*, for 609 patients – non-surgery patients were matched to surgery patients on age at diagnosis (<55 vs. ≥55 years), ER status (ER+ vs. ER-), HER2 status (HER2+ vs. HER2-), and number of metastatic sites (1 site vs. >1 site) as these variables were thought to be prognostic and related to selection for surgery. The median survival was 3.5 years (CI 2.7–5.0) in the surgery group and 3.4 years (CI 3.0–4.0) in the non-surgery group. Survival was similar after adjusting for the year of diagnosis, use of trastuzumab, and the presence of any lung metastasis (HR = 0.94, CI 0.83–1.08, $p = 0.38$) [17].

Recent published retrospective study of Huang *et al.* showed that patients in the surgery arm had long survival (median 35 vs. 22 months, $p = 0.006$). In addition, stratified analysis showed that patients with bone metastasis alone or ≤3 metastasis benefit of surgery despite patients with visceral metastasis. ER, PR, and visceral metastasis were independent prognostic factors, but patients who

underwent surgery had smaller tumors and less visceral involvement [18].

Local surgery in metastatic breast cancer has become an issue of great controversy since retrospective studies published during recent years suggested a slight benefit from an operative procedure.

The percentage of metastatic breast cancer patients undergoing surgery for the primary tumor in all these series was from 37% to 61.3% [19] that shows moving forward of first treatment choice for primary metastatic breast cancer, despite the lack of randomized confirmatory data, giving the value of surgery in the presence of metastatic disease. There were differences in selection criteria of the patients through the studies, so patients undergoing surgery were more likely to be younger, with smaller endocrine responsive tumors, and more often had only a single metastatic site without visceral involvement. Therefore, the benefit of surgery may, at least partially, be attributed to selection biases, such as surgical referral of patients with better general status, less advanced primary tumors, lower burden of metastatic disease, and better response to systemic treatment [20]. Results of multivariate analyses, including all these confounding factors, consistently suggest a survival benefit for optimal local treatment of the primary tumor. A subset of patients with metastatic breast cancer who will benefit from an intensified therapeutic approach might be those with oligometastatic disease, so the population of potentially curable *de novo* stage IV disease is estimated to be 1%-10% of newly diagnosed metastatic patients [21].

Which patients could benefit most from surgery and what is its optimal timing and the best systemic treatment for these selected patients is the question that still remains [22].

Whether to operate or not on newly diagnosed metastatic breast cancer attracts more and more attention. Based on the results of retrospective studies, there was a need of their confirmation, so the prospective trials were conducted.

In a clinical trial conducted at the M.D. Anderson Cancer Center by Holmes *et al.* in 1993, patients with solitary metastases were treated with surgical resection with or without radiation therapy, followed by systemic chemotherapy and hormonal therapy. Nearly 25% of patients were alive without disease 15 years after treatment, and only two additional events occurred at a maximum follow-up of 26 years [23].

In the open-label, randomized controlled study of Badwe *et al.* was evaluated 350 patients with *de novo* stage IV breast cancer, stratified by hormone receptor expression, tumor size and type, and number of metastasis. Median follow-up was 23 months and median OS was 19.2 months in the locoregional treatment group and 20.5 months in the no-locoregional treatment group (HR 1.04, 95% CI 0.81–1.34; $p = 0.79$), and the corresponding 2-year OS was 41.9% in the locoregional treatment group and 43.0% in the

Table 1: Retrospective studies

Reference	Patients (n)	Period of diag.	Setting	Primary surgery (n)	Notes and p value
Khan <i>et al.</i> [13]	16023	1990–1993	Population based	Yes: 9162 No: 6861	Better 3-years survival in negative margins than in positive ($p < 0.001$)
Gnerlich <i>et al.</i> [14]	9734	1988–2003	Population based	Yes: 47% No: 53%	At the study period of 36 m patients who underwent surgery were less likely to die than women who did not undergo surgery ($p < 0.001$)
Singletary <i>et al.</i> [15]		1992–2002	Review of many studies		The right criteria for surgery must be selected in terms for OS
Ma <i>et al.</i> [16]	987	2004–2018	Population based	Yes: 463 No: 524	Among patients who died during follow-up, patients who underwent surgery on their primary breast tumor had a longer median survival (21.5 m) than those who did not (14 m) ($p < 0.001$)
Bafford <i>et al.</i> [9]	147	1998–2005	Population based	Yes: 61 No: 86	ER and HER2 status were independent prognostic factors for better OS in surgery group ($p < 0.001$)
Dominici <i>et al.</i> [17]	290 matched	1998–2005	Population based	Yes: 236 No: 54	3,5-year survival rate was similar between groups ($p = 0.38$)
Huang <i>et al.</i> [18]	243	2009–2017	Hospital based	Yes: 125 No: 118	ER, PR, surgical treatment, and visceral metastasis remained isolated prognostic factors for OS ($p < 0.006$)

OS: Overall survival.

no-locoregional treatment group. The study did not demonstrate the superiority of local treatment for OS in primary metastatic breast cancer, but this study also had selection bias because patients with resectable primary tumor in the breast that could be treated with endocrine therapy were randomly assigned upfront, whereas those with an unresectable primary tumor were planned for chemotherapy before randomization [24].

In the multicenter, randomized study of King *et al.* was included 127 patients who received upfront chemotherapy and 41% of them received local surgery. The study did not show statistically significant 3-years OS between groups, but the investigators believed that the efficacy of chemotherapy is an important prognostic factor in newly diagnosed metastatic breast cancer patients, and if it is effective than surgery doesn't improve survival furthermore [7].

Table 2: Prospective studies

Reference	Patients (n)	Period of diag.	Setting	Primary surgery (n)	Notes and p value
Holmes <i>et al.</i> [23]	220	1974–1982	Hospital based	Surgery + chemo. (FAC) 134 Surgery + chemo. (VACP) 86	5-years OS: 39% versus 43%, 10-years OS: 28% and not reached Median OS: 80% and not reached
Badwe <i>et al.</i> [24]	350	2005–2013	Hospital based	Yes: 173 No: 177	2-year OS was 41.9% in the locoregional treatment group and 43.0% in the no locoregional treatment group ($p = 0.79$)
King <i>et al.</i> [7]	127	2009–2012	Multicenter based	Yes: 112 No: 15	Chemotherapy is effective prognostic factor, besides study did not confirm the role of surgery
Soran <i>et al.</i> [6]	274	36–40 months	Multicenter based	Yes: 138 No: 136	Hazard of death was 34% lower in locoregional treatment group ($p = 0.005$)

The MF07-01 phase III, randomized, controlled, and multicenter study comparing locoregional treatment followed by systemic therapy with systemic therapy alone for treatment-naïve stage IV breast cancer patients showed 34% lower Hazard of death in the locoregional treatment group than in the systemic therapy group ($p = 0.005$). The current trial did not show statistically significant improvement in 36-month survival of upfront surgery for stage IV breast cancer patients. However, a longer follow-up study (median, 40 months) showed statistically significant improvement in median survival for upfront surgery in younger patients, bone-only metastasis, and ER-positive patients [6].

Prospective studies did not show any powerful results that would lead the treatment in *de novo* stage IV breast cancer. They also had few limitations like short follow-up period (between 23–40 months), younger patients, ER-positive/HER2-negative tumors and type of chemotherapy given or not upfront.

Our patients presented in this study had surgery of the primary in the breast as the first treatment of choice. They had a ductal histopathological type, and all of them were LUMINAL A biological type. On the other hand, the tumor size was T2, so the tumor was from 2 sm to 4 sm, small tumors that allowed surgery of the primary. Hence, the patients had favorable features according to tumor biology and size and the expectation of better survival. All of them had diffuse osteolytic bone metastasis, but during the evaluation period of 36 months, it did not affect the survival. Our patients with small primary and favorable biological breast cancer type, besides diffuse bone metastasis had benefit from upfront surgery.

Breast cancer is clinically and biologically heterogenic disease, so the outcomes of the Novo stage IV breast cancer vary with molecular subtype (ER, PR, and HER2 status), tumor size, the site of metastatic disease, number of metastatic lesions, effect of systemic therapy and the age of the patient.

Conclusion

The effect of upfront surgery in newly metastatic breast cancer patients is still challenging, so there is a need to identify the exact cohort of patients who could benefit from surgery. According to this treatment, choice should be derived individually for each patient taking into account his performing status, type of metastasis and the intent of treatment – curative or palliative.

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