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## Surgery in Metastatic Breast Cancer: Revisiting its Role

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### Introduction

Metastatic breast cancer has long presented a significant challenge for the multidisciplinary care team. The management of metastatic breast cancer has traditionally relied on systemic treatments such as chemotherapy, hormonal therapy and targeted agents with surgery reserved for local control and palliation. However, advances in treatment have led to significant improvements in disease control and survival. With that, the role and timing of Loco-Regional Therapy (LRT) in selected patients, which includes surgery and radiotherapy, has remained a topic of ongoing debate and investigation [1].

Traditionally, surgery in the context of metastatic breast cancer has been employed primarily for palliative purposes - to alleviate symptoms associated with the primary breast tumor and improve quality of life. A retrospective cohort study using data from the 1988 to 2003 SEER program [2] revealed that the extirpation of the primary tumor in patients with stage IV breast cancer was associated with a significant reduction in mortality; however retrospective studies are inherently flawed by selection bias. Additionally, this study predates contemporary, highly effective, systemic therapies. However, despite its flaws, this study raised important questions.

Approximately 2.4-6% [3] of patients present with de-novo metastatic disease at their initial diagnosis, and these patients generally have poorer survival outcomes. The optimal approach to LRT in this subset of patients is still unclear. Critical questions include the precise value of LRT, the best methods of delivering it (whether through surgery, radiotherapy, or a combination of both), the optimal timing for such interventions, and the patient population most likely to benefit from it [4]. Understanding the interplay of multifactorial treatment strategies will help in improving patient outcomes with de-novo metastatic breast cancer.

### Emerging Evidence and Changing Perspectives

Several clinical trials have contributed to unraveling the complex landscape of local treatment options for metastatic breast cancer. The Japan Clinical Oncology Group Study (JCOG1017) aimed to determine if primary tumor resection with systemic therapy improved overall survival compared to systemic therapy alone in patients who responded to initial systemic treatment [5]. Between November 2011 and May 2018, 407 eligible patients with de-novo Stage IV breast cancer were randomized to either group. The study found no significant difference in overall survival between the two arms ( $p = 0.1283$ ). There was a significant improvement in survival outcomes when primary tumor resection

was employed for ER-positive tumors, pre-menopausal women and patients with solitary-organ metastasis. Primary tumor resection only demonstrated local disease control and was not suitable for all patients who had de-novo metastatic breast cancer. These findings underscore the importance of tailoring treatment strategies based on individual tumor biology and patient characteristics in metastatic breast cancer.

Researchers at Tata Memorial Centre, Mumbai, India, conducted a randomised controlled trial by including 350 women with de-novo metastatic breast cancer over the period of Feb 2005 to Jan 2013 [6]. They investigated the impact of LRT on overall survival in previously untreated women  $\leq 65$  years old. Patients were randomly assigned to receive LRT directed at the primary breast tumor and axillary lymph nodes versus no LRT treatment. Results showed that there was no significant difference in median overall survival between the groups (19.2 months with LRT treatment vs. 20.5 months without,  $p = 0.79$ ). One important point, in order to be randomized, patients who were given pre-operative chemotherapy had display objective tumor response. The study concluded that LRT treatment did not improve survival outcomes, and it was determined that it should not be routine practice in these patients who responded to initial chemotherapy, reinforcing the need to prioritize systemic therapy over LRT interventions in the treatment protocol for de-novo metastatic breast cancer.

The MF07-01 Turkish phase III randomized trial included 265 patients, comparing loco-regional surgery followed by Systemic Therapy (LRS + ST) versus Systemic Therapy (ST) alone in treatment-naive stage IV breast cancer patients [7]. The median survival was found to be 46 months (around 4 years) in the LRS + ST group compared to 35 months (around 3 years) in the ST group, with a 29% lower hazard of death in the LRS + ST group ( $p = 0.0003$ ). These findings suggested that LRS followed by ST may offer a significant survival advantage and should be considered in treatment discussions for patients with de-novo stage IV BC. On the other hand, it would be unusual to operate on patients with metastatic disease without first having some evidence of systemic control, making this trial difficult to implement widely.

The study conducted by Khan SA, et al. assessed the overall survival of early LRT for intact primary tumors in patients with metastatic breast cancer between Feb 2011 and July 2015 [8]. More in line with contemporary practice, participants received systemic therapy initially and were then randomized to receive either LRT therapy or continue systemic therapy. Results from 256 randomized patients showed no significant difference in 3-year Overall survival rates between those who received early LRT (68.4%) and those who continued systemic therapy (67.9%) ( $p = 0.57$ ). LRT reduced locoregional progression rates (16.3% vs 39.8%,  $P < .001$ ) but did not impact overall quality of life; in fact, reported overall quality of life was slightly better at 18 months in the no surgery group. No subset group showed a better overall survival based on age, hormone receptor, HER2 status or metastatic patterns. They concluded that early LRT was highly unlikely to improve the survival benefit in metastatic breast cancer patients, and unfortunately did not provide quality of

life improvements in unselected patients.

## Discussion

Despite initial retrospective studies suggesting a potential survival benefit with primary tumor resection in stage IV breast cancer patients, randomized controlled trials have yielded unimpressive results, necessitating a reevaluation of its clinical utility. Patients with de-novo metastatic breast cancer have highly variable survival outcomes associated with select disease-related variables. Refined staging models could serve as a valuable tool for clinicians to better estimate prognosis and tailor treatment strategies [9].

The divergent outcomes across the aforementioned trials highlight the complexity of managing metastatic breast cancer. Of the published trials, only one (the Turkish Federation's MF07-01) reported improved overall survival with LRT [5-8]. While LRT does not seem beneficial, in practice, it may still have a role in women who have local progression necessitating surgery. At present, guidelines consider surgery after initial systemic treatment for palliation of symptoms (i.e. pain) or for those with impending complications (i.e. open wounds or bleeding) [10]. It is recommended that surgery is only undertaken if complete local clearance may be obtained and if other sites of disease do not pose immediate risk. Multidisciplinary team input for systemic therapy management around surgery and patient understanding and engagement in the decision-making process are critical. Future studies should focus on refining patient selection criteria, defining the appropriate timeline for local treatment and sequencing with systemic therapy, and exploring novel therapeutic combinations to optimize outcomes in this challenging patient population.

## References

1. Khan SA, Stewart AK, Morrow M. Does aggressive local therapy improve survival in metastatic breast cancer? *Surgery*. 2002; 132: 620-626.
2. Gnerlich J, Jeffe DB, Deshpande AD, Beers C, Zander C, Margenthaler JA. Surgical removal of the primary tumor increases overall survival in patients with metastatic breast cancer: Analysis of the 1988-2003 SEER data. *Ann Surg Oncol*. 2007; 14: 2187-2194.
3. Wu SG, Zhang WW, Sun JY, Li FY, Lin HX, Zhou J, et al. The survival benefits of local surgery in stage IV breast cancer are not affected by breast cancer subtypes: A population-based analysis. *Oncotarget*. 2017; 8: 67851-67860.
4. Liu B, Liu H, Liu M. Aggressive local therapy for de novo metastatic breast cancer: Challenges and updates (Review). *Oncol Rep*. 2023; 50: 163.
5. Shien T, Nakamura K, Shibata T, Kinoshita T, Aogi K, Fujisawa T, et al. A randomized controlled trial comparing primary tumour resection plus systemic therapy with systemic therapy alone in metastatic breast cancer (PRIM-BC): Japan Clinical Oncology Group Study JCOG1017. *Jpn J Clin Oncol*. 2012; 42: 970-973.

6. Badwe R, Hawaldar R, Nair N, Kaushik R, Parmar V, Siddique S, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: An open-label randomised controlled trial. *Lancet Oncol.* 2015; 16: 1380-1388.
7. Soran A, Ozmen V, Ozbas S, Karanlik H, Muslumanoglu M, Igci A, et al. Primary surgery with systemic therapy in patients with de Novo stage IV breast cancer: 10-year follow-up; Protocol MF07-01 randomized clinical trial. *J Am Coll Surg.* 2021; 233: 742-751.
8. Khan SA, Zhao F, Goldstein LJ, Cella D, Basik M, Golshan M, et al. Early local therapy for the primary site in de Novo stage IV breast cancer: Results of a randomized clinical trial (EA2108). *J Clin Oncol.* 2022; 40: 978-987.
9. Plichta JK, Thomas SM, Hayes DF, Chavez-MacGregor M, Allison K, de Los Santos J, et al. Novel prognostic staging system for patients with de Novo metastatic breast cancer. *J Clin Oncol.* 2023; 41: 2546-2560.
10. Gradishar WJ, Moran MS, Abraham J, Abramson V, Aft R, Agnese D, et al. NCCN guidelines® insights: Breast cancer, Version 4.2023. *J Natl Compr Canc Netw.* 2023; 21: 594-608.