Surgery of the Primary Tumor in *de novo* Metastatic Breast Cancer: A Palliative Approach or a Potential Survival Game-Changer?

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Approximately 5–10% of primary breast cancer cases present as *de novo* stage IV disease, characterized by distant metastases at diagnosis. Traditionally, systemic therapies such as chemotherapy, endocrine therapy and targeted treatments have formed the cornerstone of treatment for metastatic breast cancer (MBC), focusing on disease control, symptom palliation and quality of life improvement. While systemic therapies remain crucial, the role of local treatments, particularly surgery for the primary tumor, is increasingly debated. Historically viewed as a palliative intervention, surgery for the primary tumor aimed to address symptoms such as bleeding, ulceration and pain. However, emerging evidence suggests that surgical resection could offer survival benefits in specific patient subgroups, such as those with limited metastatic burden or bone-only metastases. Retrospective studies and meta-analyses indicate potential survival advantages but randomized trials have produced mixed results. These discrepancies highlight the complexity of surgery's role in MBC management influenced by factors such as cancer subtype, metastatic pattern and systemic treatment response. Personalized treatment strategies are mandatory for optimizing outcomes in *de novo* MBC. Surgery of the primary tumor should not be universally applied but considered for select patients based on clinical and molecular factors. Collaboration within multidisciplinary teams is essential to integrating surgery into comprehensive care plans. Future research, including nuanced and appropriate clinical trials, is needed to define the role of surgery in prolonging survival and enhancing quality of life for patients with *de novo* MBC.

Keywords: breast cancer; breast cancer surgery; metastatic breast cancer; surgical oncology; breast surgery; *de novo* metastatic breast cancer

Introduction

Approximately 5–10% of primary breast cancer patients present *de novo* stage IV breast cancer. The management of *de novo* metastatic breast cancer (MBC), characterized by the presence of distant metastases at the time of diagnosis, has traditionally relied on systemic therapies such as chemotherapy, endocrine therapy and targeted treatments. These therapies are designed to control disease progression, alleviate symptoms and improve the patient's overall quality of life. Despite the advancements in systemic treatments, MBC remains an incurable condition and the treatment approach continues to focus on extending survival and maintaining well-being [1,2].

While systemic therapies remain the cornerstone of treatment, the role of local treatments, especially surgery for the primary breast tumor, has been a topic of increasing interest and debate. Historically, surgery has been viewed as a purely palliative intervention aimed at alleviating symptoms such as bleeding, ulceration and pain, particularly in patients with extensive metastatic disease. However, emerging evidence suggests that surgical resection of the primary tumor could offer more than just symptom relief. Recent studies have raised the intriguing possibility that surgery might provide additional survival benefits in certain subsets of patients with *de novo* MBC.

This shift in perspective has prompted a growing body of research aimed at better understanding the potential impact of surgery of the primary breast tumor on survival outcomes in *de novo* MBC. The question remains whether surgery, in combination with systemic therapies, could be a valuable strategy for prolonging survival and improving outcomes for some patients, or if its benefits are limited to specific clinical scenarios. As the field continues to evolve, understanding the nuanced role of surgery in the treatment of *de novo* MBC is critical for clinicians aiming to provide the best possible care for their patients.

The Traditional Approach: Systemic Therapy as the Gold Standard in *de novo* MBC

Metastatic breast cancer is widely regarded as a systemic disease and the standard treatment approach includes

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chemotherapy, endocrine therapy and targeted therapies aimed at controlling the widespread nature of the disease. These therapies primarily serve to palliate symptoms, as curative results in metastatic cases remain elusive for most patients [1,2].

However, the response to systemic therapies varies among patients and some individuals may experience long-term survival due to advancements in targeted treatments and immunotherapy. This variability has led to the hypothesis that more aggressive local treatments, such as surgery, might offer survival benefits.

Several studies have suggested that surgically removing the primary tumor may lead to prolonged survival, even in the presence of systemic metastases [1–8].

This has sparked a growing body of research, indicating that the issue is more complex than initially thought.

Exploring the Palliative Role of Surgery for the Primary Breast Tumor in *de novo* MBC: Potential for more than just Symptom Relief

Historically, surgery for the primary tumor in MBC has been viewed as a palliative measure, primarily aimed at alleviating symptoms such as bleeding, ulceration, infection and pain, thereby improving the patient's quality of life [1,3]. However, recent studies have challenged this traditional perspective, suggesting that surgery might offer more than just symptomatic relief and could potentially contribute to improved survival in certain patients with *de novo* MBC [4,5].

A notable meta-analysis, which examined 19 retrospective studies, revealed a significant survival benefit for patients undergoing surgery, with a pooled hazard ratio (HR) of 0.65 (95% confidence interval [CI], 0.60–0.71), indicating that surgery may improve overall survival compared to systemic therapy alone [4]. Other studies have reported similar findings, supporting the notion that surgical intervention may offer potential benefits in the management of MBC [5–8]. However, it is important to note that these retrospective studies are subject to inherent selection bias, which can complicate the interpretation of the results. Patients who undergo surgery are often those with less aggressive disease or better systemic control which may influence the outcomes and lead to an overestimation of the benefit. While the data is promising, caution must be exercised when interpreting these findings and further research is needed to fully understand the role of surgery in improving survival for patients with MBC.

Randomized Prospective Trials on Role of Surgery for the Primary Breast Tumor in *de novo* MBC: Still Seeking a Definitive Answer

While retrospective data points to potential benefits, the results from prospective randomized trials have been more ambiguous. Four key trials have attempted to determine whether surgery of the primary breast tumor in *de novo* MBC improves survival outcomes in *de novo* MBC:

- The Turkish MF07-01 trial randomized 274 patients to either locoregional treatment followed by systemic therapy or systemic therapy alone. While the study found improved survival with locoregional treatment (46 months vs. 35 months, $p = 0.005$), an imbalance in tumor subtypes between the two groups raises questions about the reliability of the findings [9].
- A study conducted in India randomized 350 patients with *de novo* stage IV breast cancer to either locoregional treatment (surgical resection of the primary tumor) or no locoregional treatment. After a median follow-up of 23 months, the study found no significant survival difference between the two groups (19.2 months vs. 20.5 months, $p = 0.79$) [10].
- The Austrian Breast and Colorectal Cancer Study Group 28 (ABCSG28) POSYTIVE trial failed to demonstrate a survival benefit from locoregional treatment. The study was prematurely halted due to poor recruitment, and its results (survival of 34.6 months vs. 54.8 months, $p = 0.267$) did not support surgery's role in extending survival in this cohort [11].
- The ECOG E2108 trial in the USA, one of the largest studies to date, enrolled 256 patients with *de novo* stage IV breast cancer who had no disease progression after 4–8 months of systemic therapy. Patients were randomly assigned to either early local therapy or continued systemic therapy. After a median follow-up of 53 months, no significant difference in survival was observed between the two groups (54.9 months vs. 53.1 months, $p = 0.57$). Notably, survival was reduced in patients with triple-negative breast cancer in the local therapy arm, while no such trend was observed in other subtypes, suggesting that surgery's benefit may vary by cancer subtype [12].

These trials underscore the complexity of interpreting breast surgery's role in *de novo* MBC. While some studies suggest benefits, others fail to show any survival advantage. Additionally, subgroup analyses based on molecular subtypes suggest that surgery may offer survival benefits for specific populations such as those with hormone receptor-positive breast cancer but not for those with triple-negative breast cancer [13].

The Potential Role of Surgery of the Primary Breast Tumor for Specific Groups in *de novo* MBC

A recent meta-analysis of the four major prospective randomized trials confirmed that surgery of the primary tumor does not provide a significant survival benefit when compared to systemic therapy alone (HR, 0.97; 95% CI, 0.72–1.29). Subgroup analyses based on breast cancer subtypes, including triple-negative, hormone-receptor-positive

and Human Epidermal Growth Factor Receptor 2 (HER2)-positive cancers, revealed no significant survival differences, suggesting that surgery may not provide a benefit for the majority of metastatic patients [14].

However, emerging evidence highlights that certain groups of patients with *de novo* MBC, particularly the oligometastatic ones with bone-only metastases, might derive a survival advantage from surgical resection of the primary tumor [15,16].

A promising study from the BOMET MF14-01 registry, a non-randomized prospective study, demonstrated that primary surgery significantly improved survival for patients with *de novo* stage IV breast cancer and bone metastasis, after adjusting for potential confounders (HR 0.40, 95% CI 0.30–0.54, $p < 0.0001$) [17]. While these findings are not from a randomized trial, they suggest that surgery may be beneficial in patients with limited metastatic burden such as those with bone-only metastasis.

This emerging evidence underscores the need for personalized treatment approaches. Surgery of the primary tumor should not be viewed as a universal treatment option for all patients with *de novo* MBC but rather as a potential strategy for specific clinical scenarios.

Additional randomized trials exploring surgery's role in different metastatic patterns and molecular profiles are essential to confirm these observations and refine treatment strategies.

The Future of Surgery for the Primary Breast Tumor in *de novo* MBC: Exploring Its Potential as a Game-Changer

As the treatment landscape for MBC continues to evolve, surgery should not be dismissed as an option. Advances in systemic therapies, particularly targeted therapies and immunotherapy, have already improved the outlook for many MBC patients. However, surgery of the primary breast tumor may still be a key component in the management of selected patients, especially those with limited metastatic burden or those who respond well to systemic therapy [18–20].

Moving forward, the challenge lies in identifying the right candidates for surgery. This requires more nuanced clinical trials incorporating molecular profiling, disease site analysis and patient performance status. Surgeons must balance the current evidence with a clinical approach tailored to each patient's specific situation, carefully weighing the potential risks and benefits of surgery in the broader treatment plan.

Practical Considerations for Breast Surgeons in Managing *de novo* MBC

When managing patients with *de novo* MBC, breast surgeons face unique challenges and considerations that influence their approach to surgery. As the role of surgery of the primary breast tumor in this setting continues to evolve, it is essential for breast surgeons to balance clinical evidence with individualized patient care.

The following key points outline the most important factors that should guide surgical decisions in MBC:

- Palliative role of surgery: surgery for the primary breast tumor in *de novo* MBC has traditionally been considered a palliative intervention. Its primary purpose is to alleviate distressing symptoms such as bleeding, ulceration, infection, and pain, which can significantly compromise a patient's quality of life. Although surgery does not offer curative potential in the metastatic setting, it can provide meaningful symptom relief and improve patient comfort. This role is particularly relevant for patients experiencing significant tumor-related morbidity, where surgical resection can reduce the need for more aggressive systemic therapies or recurrent hospitalizations. For patients with symptoms that are difficult to manage through chemotherapy or other treatments, surgery can provide substantial benefit by directly addressing the tumor.
- Importance of appropriate patient selection: while surgery may play a role in improving quality of life, it should not be viewed as a universal treatment for all patients with MBC. Careful patient selection is critical to ensuring that surgery is performed in those who are most likely to benefit. Factors such as the extent of metastatic disease, the patient's response to systemic therapies and the overall prognosis must all be considered. Surgery of the primary breast tumor is generally more effective in patients with limited metastatic burden where the disease is more likely to be controlled through both systemic treatment and locoregional therapy. Patients with stable systemic disease or those who have shown a good response to chemotherapy, endocrine therapy or targeted therapies may also be suitable candidates for surgical resection. Moreover, cancer subtype significantly impacts the effectiveness of surgery. Hormone receptor-positive tumors, for example, may benefit more from locoregional treatment, as these tumors tend to respond better to endocrine therapies. Conversely, more aggressive subtypes such as triple-negative or HER2-positive breast cancer may not derive as much benefit from early surgical interventions. These subtypes often require more intensive systemic therapies and surgery may not have the same potential to alter the disease course. Therefore, a nuanced, individualized approach to selecting candidates for surgery is necessary.
- Staying informed with ongoing research: as the treatment landscape for MBC continues to change, staying updated on the latest research is essential for breast surgeons. The growing body of literature on the role of surgery in metastatic disease suggests that personalized approaches which combine systemic therapies with surgical intervention, are increasingly important in improv-

ing patient outcomes. New clinical trials, emerging data on molecular profiling and advancements in targeted therapies may influence the role of surgery in specific patient populations. Surgeons should be proactive in understanding and incorporating the latest evidence into their practice, particularly as systemic therapies continue to evolve. Staying up-to-date with ongoing research can help shape treatment strategies, refine indications for surgery and ultimately enhance patient care.

- Considering overall health and patient preferences: when making decisions about surgery in MBC, it is crucial to consider the patient's overall health, performance status and preferences. For some patients, surgery may provide significant physical and emotional benefits, even if it does not offer a survival advantage. The ability to manage symptoms such as pain, bleeding or ulceration can improve the patient's daily functioning and overall sense of well-being. Equally important is understanding the patient's goals for treatment. Some patients may prioritize quality of life over the potential for survival extension while others may seek aggressive interventions to prolong their life expectancy. Open, honest discussions between surgeons and patients about the risks and benefits of surgery, as well as the possible outcomes of systemic therapies, are essential in making an informed, patient-centered decision.
- Collaborative multidisciplinary approach: given the complexity of MBC, an integrated multidisciplinary approach is crucial to developing an effective treatment strategy. Surgery of the primary breast tumor represents just one component of a comprehensive care plan and must be incorporated into a broader strategy that includes oncologists, radiation therapists, palliative care teams and other dedicated professionals. Breast surgeons should work closely with a wide range of specialists to ensure that the treatment plan is tailored to each patient's unique needs and specific disease characteristics. This collaborative approach ensures the patient receives the most effective combination of systemic therapies, local treatments and supportive care. Multidisciplinary teamwork is particularly important in MBC management, as it provides a holistic approach to patient care, optimizing outcomes across all aspects of treatment and well-being.

Conclusions

The role of surgery for the primary breast tumor in *de novo* metastatic breast cancer remains a complex and contentious issue. While systemic therapies remain the cornerstone of management, emerging evidence suggests that surgical resection of the primary tumor may benefit select patient populations. However, definitive answers are still lacking, emphasizing the need for personalized treatment approaches and further research. Surgery may offer survival benefits for patients with limited metastatic burden, such as bone-only metastasis, or those who respond well to systemic therapies. In contrast, aggressive subtypes may not benefit as much, highlighting the importance of molecular profiling and patient selection. Future treatment decisions should be guided by collaboration across specialties, considering tumor biology, disease extent, and patient-specific factors.

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Not applicable.

Author Contributions

GF conceived and designed the editorial; GF collected and analyzed the relevant literature; GF wrote and revised the manuscript critically for intellectual content. GF gave final approval of the version to be published. GF has participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

Gianluca Franceschini is serving as one of the Editorial Board members of this journal. The author declares that Gianluca Franceschini had no involvement in the peer review of this article and has no access to information regarding its peer review.

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