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Editorial

Oligometastatic breast cancer: back to square one in the era of precision oncology

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INTRODUCTION

Metastatic breast cancer (MBC) has long been considered the paradigm of an incurable systemic disease. Once distant dissemination occurs, therapeutic strategies have traditionally focused on disease control, symptom palliation, and survival prolongation rather than cure. Yet, as systemic therapies become increasingly effective and diagnostic tools more sensitive, the classical distinction between localized and metastatic disease appears progressively less absolute.

Within this evolving landscape, the concept of oligometastatic disease has emerged as a possible intermediate biological state between localized and widely disseminated cancer. Originally proposed more than two decades ago, the oligometastatic paradigm suggests that a subset of patients with limited metastatic burden may experience prolonged survival and, in selected cases, durable disease control when treated with a combination of systemic and local therapies.[1]

However, despite its growing clinical relevance, oligo-MBC remains a concept that is easier to invoke than to define.

Most current definitions rely predominantly on morphological criteria, typically based on the presence of a limited number of metastatic lesions-most commonly up to five-detected on imaging studies. Yet this approach inevitably raises a fundamental question: does oligometastatic disease represent a biologically distinct state characterized by limited metastatic competence, or is it simply an early radiological manifestation of a process that is, by its very nature, already systemic?

THE CONTROVERSIAL ROLE OF SURGERY IN DE NOVO METASTATIC DISEASE

Few issues illustrate the uncertainty surrounding oligo-MBC better than the long-standing debate on the role of locoregional treatment of the primary tumor in patients presenting with de novo stage IV disease.

Historically, surgical intervention in this setting has been considered primarily palliative, aimed at controlling local complications such as bleeding, infection, or ulceration. Nevertheless, several retrospective studies and meta-analyses have reported an association between surgical removal of the primary tumor and improved survival outcomes in selected patients with MBC.[2,3]

While these observations have generated considerable interest, their interpretation must remain cautious. Retrospective analyses are intrinsically affected by selection bias, as patients undergoing surgery often have more favorable clinical characteristics, including lower metastatic burden, better performance status, and tumors with more indolent biological behavior.

Prospective randomized trials have attempted to clarify this issue, yet their findings have been inconsistent. The Turkish MF07-01 trial reported a survival advantage associated with locoregional treatment of the primary tumor.[4] In contrast, other randomized studies-including the Tata Memorial trial, the ABCSG-28 POSYTIVE study, and the ECOG-ACRIN E2108 trial-failed to demonstrate a significant survival benefit from surgery in this setting.[5-7]

Interpreting these results is challenging for several reasons. First, the patient populations enrolled in these trials are highly heterogeneous in terms of tumor biology, metastatic burden, and response to systemic therapy. Second, and perhaps more importantly, many of these studies were conducted in therapeutic contexts that no longer fully reflect contemporary standards of care. Over the last decade, the therapeutic landscape of MBC has changed profoundly with the introduction of highly effective systemic treatments including dual HER2 blockade, CDK4/6 inhibitors, antibody–drug conjugates, and immunotherapy.[8]

These advances have substantially altered the natural history of metastatic disease and may modify the relative contribution of locoregional interventions.

Evidence derived from real-world clinical practice further illustrates this complexity. In retrospective series of patients with de novo stage IV breast cancer, surgery of the primary tumor has been associated with longer overall survival in hormone receptor-positive and HER2-positive subtypes, whereas no clear benefit appears to emerge in triple-negative disease.[3] Interestingly, the greatest survival advantage has been observed in patients who underwent surgery after achieving prolonged disease control with systemic therapy, suggesting that treatment response itself may represent an important criterion for patient selection.

Taken together, these findings suggest that the potential benefit of surgery is unlikely to be universal across all patients with MBC. Rather, locoregional treatment may confer an advantage only in carefully selected patients with biologically more indolent disease. The central challenge, therefore, lies in identifying these patients prospectively, as surgery itself cannot serve as a tool to reveal tumor biology.

OLIGOMETASTASIS AS A BIOLOGICAL SPECTRUM

The conceptual basis of oligometastatic disease originates from the spectrum theory proposed by Hellman and Weichselbaum, according to which metastatic dissemination should be understood as a continuum rather than a binary event.[1] Within this framework, tumors may exist in intermediate biological states characterized by limited metastatic competence, where the ability to generate widespread dissemination remains incomplete.

In clinical practice, however, the identification of oligo-MBC continues to rely largely on imaging findings. As highlighted in recent literature, one of the major limitations in this field is the absence of robust biomarkers capable of distinguishing true oligometastatic biology from early systemic dissemination.[9]

This limitation may partly explain why local ablative strategies-including surgery, stereotactic radiotherapy, and other focal treatments-have produced heterogeneous and sometimes contradictory results across clinical studies. Without a reliable biological definition, the population labeled as oligometastatic inevitably remains heterogeneous.

THE WEIGHT OF TUMOR BIOLOGY

The intrinsic heterogeneity of breast cancer further complicates the interpretation of available current evidence. Molecular subtype plays a crucial role in determining metastatic behavior, treatment response, and survival outcomes.

Hormone receptor–positive tumors generally follow a more indolent clinical course and may remain controlled for prolonged periods with endocrine-based therapies. HER2-positive disease has experienced a remarkable improvement in prognosis following the introduction of highly effective targeted treatments.[8] In contrast, triple-negative breast cancer typically exhibits a more aggressive biological behavior characterized by earlier relapse and shorter survival, and appears to derive limited benefit from locoregional interventions.

These biological differences strongly suggest that oligo-MBC should not be viewed as a single clinical entity. Rather, it likely represents a heterogeneous condition whose biological meaning varies substantially across molecular subtypes.

RETHINKING FOLLOW-UP IN THE ERA OF PRECISION ONCOLOGY

The evolving concept of oligometastatic disease also raises important questions regarding follow-up strategies for breast cancer survivors. Current surveillance recommendations are intentionally non-intensive and rely largely on clinical evaluation, based on historical randomized trials that failed to demonstrate survival benefits associated with the early detection of asymptomatic metastatic disease.[10]

However, the therapeutic landscape of MBC is rapidly evolving. Novel systemic treatments-including antibody-drug conjugates, targeted agents, and immunotherapy-have demonstrated increasing efficacy, particularly when administered at earlier stages of disease progression. This

concept may be particularly relevant in triple-negative breast cancer, where immunotherapy appears to be more effective before the development of advanced mechanisms of immune escape.[11]

In this context, earlier detection of metastatic relapse-especially when confined to a limited oligometastatic state-may acquire renewed clinical significance. Emerging technologies such as circulating tumor DNA (ctDNA) analysis now offer the possibility of detecting minimal residual disease long before radiological progression becomes evident.[12]

The integration of liquid biopsy into clinical practice may therefore open a new paradigm in which molecular evidence of residual disease guides closer imaging surveillance and potentially earlier therapeutic interventions.

A NEW PERSPECTIVE: BIOLOGY-GUIDED SURGERY

Future strategies may progressively move beyond purely anatomical definitions of oligometastatic disease toward biologically informed models of patient selection. Within such a framework, biomarkers such as ctDNA dynamics or minimal residual disease detection could help identify patients with limited systemic dissemination who might benefit from aggressive local treatments, including surgery or ablative radiotherapy.

Rather than relying exclusively on the number or anatomical distribution of metastatic lesions, treatment decisions may increasingly incorporate biological indicators reflecting tumor behavior and the degree of systemic disease control.

BACK TO SQUARE ONE

Paradoxically, despite decades of research, the management of oligo-MBC may still remain at an early stage of conceptual development. The fundamental question remains unresolved: does oligometastatic disease represent a potentially curable biological state, or does it simply correspond to the earliest detectable phase of systemic dissemination?

Current evidence increasingly suggests that the answer may lie not in the number of metastases but in the underlying biology of the tumor. Until reliable biomarkers capable of identifying tumors with genuinely limited metastatic competence become available, the concept of oligo-MBC will remain largely a clinical construct.

In the era of precision oncology, the real challenge may therefore be not simply how to treat oligometastatic disease more aggressively, but how to define it biologically.

Only when molecular tools-such as ctDNA dynamics, minimal residual disease detection, and integrated genomic profiling-allow clinicians to identify patients with truly limited metastatic potential will it become possible to determine whether surgery and other local treatments can meaningfully modify the natural history of MBC.

Until then, the field may indeed find itself back to square one—reconsidering not only how oligo-MBC should be treated, but whether we have been defining it correctly all along.

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