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Review Article

To Rebiopsy or Not? Current Evidence and Ongoing Controversies in Metastatic Breast Cancer Care

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Abstract

Rebiopsy in metastatic breast cancer (MBC) is increasingly recognized as an important step in optimizing treatment decisions. This review summarizes current evidence, biological rationale, and practical considerations regarding rebiopsy in MBC. Receptor discordance between primary and metastatic lesions, reported in approximately 10–40% for estrogen receptor (ER), 20–30% for progesterone receptor (PR), and 5–15% for human epidermal growth factor receptor 2 (HER2), may result in clinically meaningful changes in systemic therapy. Although international guidelines recommend rebiopsy at recurrence or metastatic presentation, its implementation remains limited by procedural risks, sampling bias, and logistical constraints. Rebiopsy provides valuable insights into tumor evolution and supports personalized treatment strategies; however, its use should be individualized, balancing potential benefits and risks within a multidisciplinary framework.

Keywords: Breast cancer, Metastatic Breast Cancer, Biopsy, Receptor status, Personalized medicine

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All relevant data are within the paper and its Supporting Information files.

Introduction

Metastatic breast cancer (MBC) remains one of the most difficult clinical situations[1,2] with up to 30% of patients with early-stage breast cancer developing MBC[1]. The heterogeneity of breast cancer, including receptor status discordance between primary and metastatic disease, makes therapeutic selection a challenge.[2] The rate of discordance for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) between primary and recurrence was 19%, 34%, and 15%, respectively. These variations can influence therapeutic approaches, therefore emphasizing the need to re-evaluate the biology of a tumor at the metastatic setting.[3-5]

Current international guidelines increasingly support biopsy of metastatic lesions to confirm diagnosis and reassess biomarker status, as treatment strategies are largely driven by tumor subtype.[5] However, the choice for rebiopsy is not devoid of controversy. Nevertheless, rebiopsy remains controversial due to its invasive nature, potential complications, and inconsistent evidence regarding survival benefit. Some studies have reported no significant differences in survival outcomes between patients who undergo rebiopsy-guided treatment changes and those who do not.[3] This review discusses the biological rationale, clinical implications, guideline recommendations, and ongoing controversies surrounding rebiopsy in metastatic breast cancer.

Methodology for Literature Review

This narrative review was conducted to summarize current evidence and guideline recommendations regarding rebiopsy in metastatic breast cancer. A literature search was performed in PubMed, Scopus, and Google Scholar databases for articles published

between January 2010 and May 2025. The search strategy included the keywords *"metastatic breast cancer," "rebiopsy," "receptor discordance," "HER2-low," "hormone receptor conversion,"* and *"clinical guidelines."*

Only English-language, peer-reviewed publications and major international guidelines (NCCN, ESMO, ASCO, and NICE) were included. Articles were selected based on their relevance to biological rationale, receptor discordance, clinical outcomes, and current controversies in rebiopsy practice. Case reports, conference abstracts, and non-peer-reviewed sources were excluded. Reference lists of included studies were also screened to identify additional pertinent articles.

Artificial intelligence–based tools (ChatGPT, Quillbot) were used only to assist in language refinement, summarization, and grammar editing of the manuscript. These tools were not employed to generate, analyze, or interpret any original scientific data or content. All text, ideas, and conclusions presented were conceived, verified, and approved by the authors.

Guideline Recommendations

The National Comprehensive Cancer Network (NCCN)

The NCCN Clinical Practice Guidelines in Oncology: Breast Cancer (Version 4.2025) suggested that patients with MBC should receive a biopsy from the metastatic lesion. This is recommended because evidence is available regarding changes in receptor status between primary and metastatic sites that may affect treatment selection.

Specifically, the guidelines report that a biopsy at first relapse, or first evidence of stage IV disease, is warranted in order to confirm the diagnosis and revisit biomarker status (with respect to ER, PR, and HER2, among others).[9]

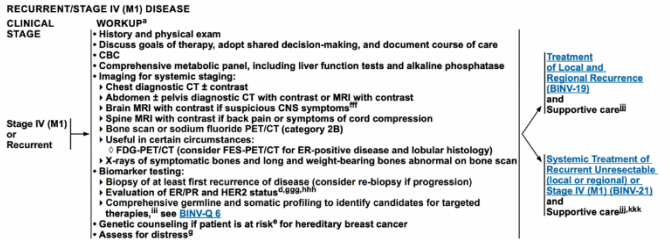

Figure 1. NCCN Guideline for Recurrent/Stage IV (M1) Breast Cancer[9]

The European Society for Medical Oncology (ESMO)

The European Society for Medical Oncology (ESMO) delivers published recommendations for the treatment of MBC, including recommendations for rebiopsy for particular patient populations. ESMO Clinical Practice Guidelines recommend biopsy of the metastasis to verify diagnosis and re-evaluate the status of biomarkers such as ER, PR, and HER2. This suggestion is predicated on data showing that the status of the receptor may differ between primary and metastatic sites, affecting the choice of therapy. In addition, ESMO notes that rebiopsy may offer valuable information to guide treatment selection, particularly with targeted treatments. For example, assessing the HER2 status in the metastatic site is indispensable to achieve the clinically relevant application of anti-HER2 regimen. The guidelines also recognize that, when biopsy is not possible, treatment decisions might be based on previous pathological reports and noninvasive tests.[19]

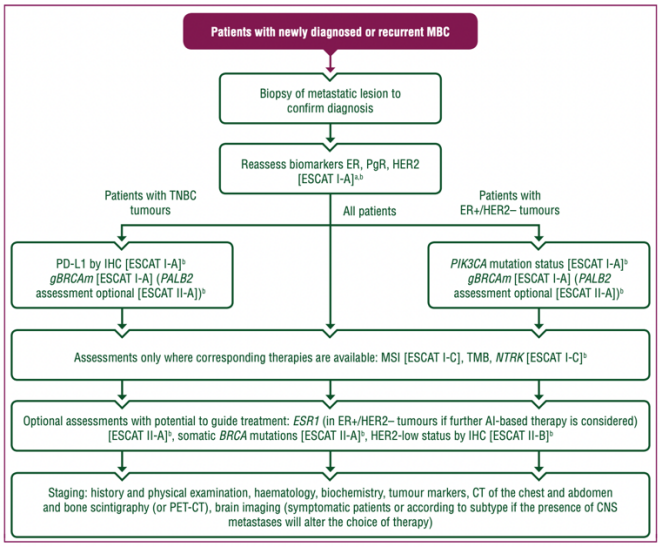

Figure 2. ESMO Guideline for Diagnostic work-up and staging metastatic breast cancer[19]

The American Society of Clinical Oncology (ASCO)

In its guidelines for MBC, the American Society of Clinical Oncology (ASCO) does not definitively advocate performing rebiopsy. It, however, recommends that treatment decisions can be made on the basis of menopausal status, pathological features, and biomarker profile, if there are high-quality results. There is an overemphasis on biomarker assessment of HER2, hormone receptors, PD-L1, and BRCA status in order to drive the choice of management: endocrine therapy, chemotherapy, or targeted therapy. However, whether these results should be derived from the rebiopsied metastatic lesion or from the primary tumor is a question the guideline did not address.[20]

The National Institute for Health and Care Excellence (NICE)

According to the National Institute for Health and Care Excellence (NICE) guidance on Advanced breast cancer: diagnosis and treatment (CG81), the current evidence and ongoing controversies around rebiopsy in metastatic breast cancer reflect a nuanced position: while older versions of the guideline advised not to perform a repeat biopsy solely to reassess known oestrogen receptor (ER) or HER2 status at recurrence, more recent surveillance and quality standards acknowledge that biopsy of recurrent or metastatic disease to reassess receptor status should be considered if it would change management, because studies show that receptor discordance between primary and metastatic lesions occurs in a meaningful minority of cases and can impact treatment decisions.[21]

NICE therefore does not mandate routine rebiopsy for all metastatic recurrences but supports the clinician's judgment and shared decision-making with the patient where rebiopsy may yield actionable information, highlighting an ongoing controversy in balancing clinical benefit, procedural invasiveness, and current evidence gaps in high-quality outcome data.[21]

Guideline	Recommendation for Rebiopsy	Key Points / Notes
NCCN (v4.2025)	Biopsy recommended at first relapse or metastatic diagnosis to re-evaluate ER, PR, HER2.	Reassess receptor status before treatment decision.
ESMO (2021)	Biopsy of metastasis recommended to verify diagnosis and biomarkers.	If not feasible, use prior pathology and imaging.
ASCO (2024)	Rebiopsy may be considered to confirm receptor status and molecular targets.	Allows biomarker-driven management without mandatory rebiopsy.
NICE (CG81)	Supports reassessment of receptor status when clinically indicated.	Encourages individualized decision-making based on patient context.

Table 1.1 Guideline recommendation

Limitations and Controversies Surrounding Rebiopsy in Metastatic Breast Cancer

Despite its potential benefits, routine rebiopsy in metastatic breast cancer remains controversial. Core needle biopsy carries a small but measurable false-negative rate, influenced by tumor heterogeneity and technical factors. Additionally, evidence regarding survival benefit from rebiopsy-guided treatment modification is inconsistent. Several studies have reported no significant differences in disease-free survival, progression-free survival, or overall survival between patients who underwent rebiopsy and those who did not. The GIM 13 AMBRA study, an observational cohort of 939 HER2-negative mBC patients, showed that 62.6% of patients had rebiopsy in case of first relapse. No difference in disease-fee, progress-free and over-all survivals was detected between both the patients who developed the shift of molecular subtypes and those who did not, however, the study underscored the necessity to reuse rebiopsy to elucidate tumor course and help make decisions of personal medical therapy.[22]

The prognosis of breast cancer patients was based on the subtype in metastases rather than that in primary disease, and liver rebiopsy should be an indispensable part of managing de novo stage IV patients with liver metastases. Combined, these results suggest rebiopsy in metastatic breast cancer to ascertain changes in receptor status, which may have an important clinical implication in the management and outcome of patients.[23-27]

Furthermore, there are risks to rebiopsy. Complications are few and infrequent, but may in particular occur when a biopsy is performed of some metastatic sites like the lung or liver (bleeding, infection, pneumothorax). These potential complications make it important to weigh the likely benefits of rebiopsy of these lesions against the risk. Rebiopsy can represent a specific challenge at certain sites of metastasis, including brain and bones. Brain metastases are frequently not biopsied for the reason that the biopsy itself is invasive and can cause safety issues in the neurological setting. Bone metastases have also been challenging to biopsy correctly since a hard tissue environment may result in a lack of adequate sampling and non-diagnostic results.[26,27]

Discussion

The management of MBC continues to evolve alongside advances in molecular oncology. Receptor discordance and tumor evolution present significant challenges but also opportunities for treatment

optimization. Rebiopsy can reveal clinically actionable changes, including conversion to HER2-low disease or loss of hormone receptor expression, which may substantially influence therapeutic strategy.[7,16,22] For instance, trastuzumab deruxtecan has been effective in HER2-low MBC (a recently defined subtype and one which often goes unrecognized in the primary tumor). Studies by Lv et al. (2022), Jin et al. (2023), and Schrijver et al. (2018) further support the need for rebiopsy for discovering biological and therapeutical relevant alterations. Moreover, differences in serum markers have also been reported to potentially influence prognosis, where patients who lose positivity to the hormone receptors suffer from a worse prognosis than those maintaining receptor expression.[6-8]

However, the recommendation for routine rebiopsy is still debated. Guidelines differ: NCCN and ESMO say rebiopsy to redefine tumor biology is indicated when rechallenge is possible; ASCO and NICE adopt a more cautious position, highlighting the biomarker-driven approach but stopping short of demanding a new biopsy. Lastly, the potential clinical implications of rebiopsy should be balanced with its constraints. Complications include those related to procedure (eg, bleeding, infection, pneumothorax) and technical issues, and difficulties in treating metastatic sites that are difficult to access (eg, brain, bone).[2,4,9,19-22]

Correct application, you should not think that rebiopsy is a must to all patients, and spent a proportion of patients should be considered carefully before performing rebiopsy. Greatest benefit could be obtained in patients where change in receptor status is likely to affect systemic treatment or eligibility to targeted agents. The use of shared decision-making, discussion on the feasibility of biopsy, and inclusion of non-invasive testing (i.e., ctDNA or liquid biopsy) may support this approach. The clinical role of rebiopsy is expected to gain more ground, particularly when incorporated in more comprehensive strategies of molecular profiling, as the therapeutic horizon broadens. Additional exploration is needed to define the criteria for rebiopsy and confirm its role in provoking a significant improvement in survival and quality of life in patients with MBC.

Conclusion

Rebiopsy in metastatic breast cancer is useful for reassessing the evolving tumor biology, particularly because receptor discordance (ER, PR, and HER2) can occur between primary and metastatic sites. These modifications can have a major impact on therapeutic decision-making particularly as new targets like HER2 low have evolved. While NCCN and ESMO guidelines generally support rebiopsy, ASCO and NICE emphasize individualized clinical judgment. Given procedural risks and variable survival benefit, rebiopsy should be selectively applied within a personalized, multidisciplinary care framework to optimize treatment outcomes in metastatic breast cancer.

Ethics approval

Not required.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

AI-based language tools, including ChatGPT and Quillbot, were utilized during the preparation of this manuscript to assist with the following:

a. Language refinement (enhancing grammar, clarity, and overall readability),

b. Content summarization (condensing findings and conclusions), and

c. Technical writing assistance (improving the structure and presentation of complex scientific descriptions).

We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

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