Review

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Advances in research on receptor heterogeneity in breast cancer liver metastasis

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SUMMARY: Breast cancer liver metastasis (BCLM) presents a critical challenge in breast cancer treatment and has substantial epidemiological and clinical significance. Receptor status is pivotal in managing both primary breast cancer and its liver metastases. Moreover, shifts in these statuses can have a profound impact on patient treatment strategies and prognoses. Research has indicated that there is significant heterogeneity in receptor status between primary breast cancer and liver metastases. This variation may be influenced by a multitude of factors, such as therapeutic pressure, inherent tumor heterogeneity, clonal evolution, and the unique microenvironment of the liver. Changes in the receptor status of BCLM are crucial for adjusting treatment strategies, and liver biopsy plays an important role in the treatment process. Directions for future research targeting changes in receptor status include in-depth study of molecular mechanisms, combined treatment strategies for receptor status reversal, development of artificial intelligence deep learning models to predict receptor status in liver metastases, and clinical research on new drug development and combination therapies. That research will provide more precise treatment strategies for patients with BCLM and improve their prognosis.

Keywords: breast cancer liver metastasis, receptor heterogeneity, influencing factors, molecular mechanisms, treatment strategies

1. Introduction

According to the latest data from the International Agency for Research on Cancer (*1*), breast cancer has become the most commonly diagnosed cancer type in women worldwide, surpassing lung cancer. The latest statistics from the American Cancer Society show that the incidence of breast cancer has been continuously rising and those affected have become younger over the past decade (*2*). The survival rate of breast cancer varies depending on the stage at diagnosis, molecular subtypes, and other clinical pathological characteristics, with a 5-year relative survival rate of 99% for localized disease and only 32% for distant metastatic disease (*2*). Distant metastasis of breast cancer is the leading cause of death in patients with breast cancer. The liver ranks among the primary targets of breast cancer metastasis. In patients with advanced breast cancer, liver metastasis occurs in 20-30% of cases. This makes the liver the third most common site of distant metastasis, following bone and the lungs (*3,4*). Notably, breast cancer liver metastasis (BCLM) also tends to develop at a younger age, with a higher incidence of liver metastatic breast cancer in young women compared to older women (*5,6*). Thus, focusing on the prognosis for patients with BCLM is crucial.

Based on molecular biological characteristics, breast cancer can be classified into Luminal A, Luminal B, Triple-negative, HER2-positive, and HER2-negative types. The status of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) is crucial in guiding clinical treatment decisions (*7*). The American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) have recently updated their clinical practice guidelines for metastatic breast cancer. These updates emphasize receptor-dependent treatment strategies, similar to those used for in situ breast cancer. Specifically, they recommend formulating personalized treatment plans based on the receptor status

of liver metastases. This approach ensures that treatment is tailored to the specific characteristics of the metastatic disease, potentially improving outcomes for patients with BCLM (*8,9*).

Clinical research has demonstrated that there is a certain degree of expression discrepancy in ER, PR, and HER2 between primary breast cancer and liver metastases (*10-12*). Therefore, re-evaluating the receptor status of BCLM is crucial to formulating precise personalized treatment plans. The molecular mechanisms of and new drug targets associated with changes in the receptor status of BCLM need to be urgently examined. The current review meticulously synthesizes recent research findings to provide a summary of the situation and potential factors influencing receptor heterogeneity in BCLM. It also delves into the impact of these factors on the development of diagnostic and treatment strategies. Additionally, it explores and discusses promising directions for future research in this critical field in order to shed light on new avenues for advancing our understanding and management of this complex condition.

2. Heterogeneity of receptor status in BCLM

Clinical studies have shown that there is a significant degree of temporal and spatial heterogeneity in the expression of ER, PR, and HER2 during the process of breast cancer metastasis (*13-20*) (Tables 1 and 2). A study by Sundén *et al*. (10) on a cohort of 132 BCLM patients registered in two Swedish national cancer registries indicated that the discordance rates for ER, PR, and HER2 status between the primary tumor and liver metastasis were 17%, 33%, and 10%, respectively; among the cases with changes in receptor status, the proportion in which ER changed from positive to negative was 72.7%, and for PR it was 86.5%. Chen *et al*. (*21*) assessed a cohort of 390 paired primary and distant metastasis cases and found that the discordance rates for ER, PR, and HER2 between the primary and metastatic sites were 20%, 41.4%, and 14.1%, respectively; among all cases with receptor changes in breast cancer distant metastasis, the proportion in which ER changed from positive to negative was 85.9%, the proportion in which PR changed from positive to negative was 77.0%, and the proportion in which HER2 changed from positive to negative was 56.8%, but this study did not specify the individual cases in which each receptor changed from positive to negative. A meta-analysis performed by Schrijver *et al*. (*11*), which encompassed 39 studies, revealed notable discordance rates for ER, PR, and HER2 of 14.3%, 47.0%, and 12.1%, respectively, in BCLM. The researchers further observed that the random effect percentages for ER, PR, and HER2 changing from positive to negative were 22.5%, 49.4%, and 21.3%, respectively. Conversely, the percentages for these receptors changing from negative to positive were found to be 21.5%, 15.9%, and 9.5%, respectively. Together, the aforementioned studies demonstrate that among the receptors in BCLM, the discordance rate for PR is the highest, while that for HER2 is the lowest. Notably, a greater proportion of patients experience a change in ER and PR expression from positive to negative, as compared to those who undergo a change from negative to positive. In contrast, the proportion of patients whose HER2 status changes from positive to negative is relatively similar to those whose status changes from negative to positive.

Interestingly, almost all studies on changes in receptor status in BCLM have indicated that the discordance rate for HER2 is the lowest between the primary breast cancer and liver metastasis, but nearly one-third of patients with BCLM have their HER2 status change from no HER2 expression in the primary tumor to low HER2 expression in the liver metastasis (*22,23*). For example, a study by Almstedt *et al*. (*24*) showed that during the process of BCLM, the discordance rate for HER2 status was 40.9%, with 72.2% changing from no HER2 expression to low HER2 expression.

In addition, certain studies have indicated that alterations in HER2 status are intimately linked to the patient's ER status. Specifically, a HER2 status of 0 is predominantly associated with ER negativity, whereas low expression of HER2 tends to occur more frequently

Table 1. Breast cancer liver metastasis receptor status conversion

	Rate of discrepancy (%)(Event/Sample size)		
	ER	PR	HER2
Curigliano *et al*., 2011	14.5 (37/255)	48.6 (124/255)	14.0 (24/172)
Hoefnagel *et al*., 2012	12.7 (8/63)	41.3 (26/63)	9.5 (6/63)
Botteri *et al*., 2012	15.2 (15/99)	-	13.3 (8/60)
Nakamura *et al*., 2013	-	-	10.0 (2/20)
Woo *et al*., 2019	16.7 (4/24)	33.3 (8/24)	16.7 (4/24)
Chen *et al*., 2020	20.0 (16/80)	41.4 (29/70)	14.1 (10/71)
Sundén *et al*., 2023	16.9 (22/130)	32.5 (37/114)	9.9 (10/101)
Procházková *et al*., 2024	20.0 (2/10)	40.0 (4/10)	0 (0/10)

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor.

Table 2. Basic characteristics of patients

	Total number	Age(years)	Gender	Adjuvant endocrine therapy (BC)	Adjuvant chemotherapy (BC)	T stage of BC (%)					N stage of BC (%)				M stage of BC (%)	
						Tis	1	2	3	4	0	1	2	3	0	1
Curigliano *et al*., 2011	255	45 (26-75)	Female	69.8	51.7	-	46.7	42.5	Total 10.8		40.2	49.2	10.6		91.2	8.8
Hoefnagel *et al*., 2012	233	-	Female	-	-	-	-	-	-	-	-	-	-	-	-	-
Botteri *et al*., 2012 (biopsied)	100	-	Female	79.0	72.0	-	45.0	45.0	Total 5		-	-	-	-	-	-
Nakamura *et al*., 2013	156	-	Female	-	-	-	-	-	-	-	-	-	-	-	-	-
Woo *et al*., 2019	152	49 (26-83)	Female	49.3	70.4	-	24.3	41.4	17.1	17.1	25.0	33.6	21.7	19.7	90.8	9.2
Chen *et al*., 2020	348	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sundén *et al*., 2023	132	60 (27-84)	Female	69.8	62.4	7.9	30.2	49.2	9.5	3.2	67.7	29.1	1.6	1.6	100.0	0.0
Procházková *et al*., 2024	50	52 (26-78)	Female	-	-	4.0	40.0	48.0	2.0	6.0	52.0	30.0	10.0	8.0	98.0	2.0

Abbreviations: BC, primary breast cancer.

in tumors that are ER-positive (*22*).

3. Factors influencing receptor heterogeneity in BCLM

3.1. Selection pressure from treatment

A whole-exome sequencing analysis of primary tumors and matched metastases (*25*) revealed that untreated metastases typically originate from the main clone of the primary tumor, while treated metastases often harbor driver mutations specific to the metastasis, mainly due to the selection pressure of drug treatment that causes metastases to derive from rare clones in the primary tumor. Several studies (*26-28*) have shown that breast cancer patients who have undergone chemotherapy or endocrine therapy have a higher rate of changes in ER or PR status when they develop distant metastases compared to those who have not received drug treatment. Niikura *et al*. (*29*) investigated the relationship between HER2-targeted therapy and HER2 changes, and their results indicated that the inconsistency between the HER2 status in primary and metastatic lesions in breast cancer is related to whether the patient received chemotherapy. Zhao *et al*. (*30*) discovered a correlation between hormone receptor conversion in distant metastases of breast cancer and prior adjuvant endocrine therapy. Specifically, over 40% of patients who underwent adjuvant endocrine therapy experienced a loss of PR in the distant metastases of breast cancer. Additionally, more than 20% of patients who had previously received adjuvant endocrine therapy exhibited a loss of ER at the metastatic sites. In addition, the aforementioned study also found a positive correlation between adjuvant chemotherapy and the loss of PR at recurrence. These statistical results are similar to those of several previous statistics (*31-33*), suggesting that receptor heterogeneity in BCLM may be associated with the selection pressure of treatment.

3.2. Clonal evolution and tumor heterogeneity

Clonal evolution refers to the process in which some mutated subclones expand under the pressure of natural selection while others may perish as the tumor cell population evolves over time. Sprouffske *et al*. (*34*) confirmed the clonal evolution process of primary breast tumors in the development of metastatic dissemination. They achieved this by tracking genetic changes in breast cancer tumor xenograft models during metastasis. In addition, several studies have proposed that distinct tumor microenvironments can exert different selective pressures, thereby influencing tumor clonal evolution (*35,36*).

Tumor genetic heterogeneity refers to the diversity of genetic variations and gene expression patterns among different cells within a tumor during its development,

which may arise through complex genetic, epigenetic, and protein modifications. Genetic heterogeneity within tumors has been extensively documented, serving as a reflection of potential clonal evolution occurring within the tumor (*37-44*). A clinical study has shown that patients with high tumor heterogeneity are more likely to have adverse prognostic outcomes (*45*). In the progression of BCLM, the diversity in receptor expression status is indicative of the high degree of tumor heterogeneity present in the metastatic lesions. A study has indicated that there may be subclones in the primary breast tumor that cannot be detected by current technical means and that changes in receptor status occur during the spread to the liver due to various factors (*46*). Moreover, successful BCLM requires multiple steps (*47-50*), each of which can produce a population bottleneck, leading to differences in receptor status between the metastatic and primary lesions.

3.3. Influence of the metastatic microenvironment

Changes in the liver microenvironment may also affect receptor heterogeneity in BCLM. These changes, such as the presence of inflammatory responses and cytokines in BCLM, may influence the phenotype of breast cancer tumor cells, including receptor status. For example, studies have shown that inflammatory factors such as IL-6 may affect cell adhesion and the expression of E-cadherin, thereby influencing tumor metastasis and receptor status (*51,52*).

4. Impact of receptor heterogeneity in BCLM on treatment strategies

Zhao *et al*. (*30*) found that patients experiencing a change in hormone receptor status from negative to positive tend to have longer survival times than those with a persistently hormone receptor-negative status. Moreover, multivariate survival analysis has revealed that patients whose ER status changes from positive to negative face a significantly elevated risk of death compared to those with a stable ER-positive status. A large cohort study (*53*) indicated that patients with low HER2 expression have improved survival rates compared to those with no HER2 expression, regardless of ER status. This phenomenon is also reflected in other studies (*54,55*). Clearly, changes in receptor status during the progression of breast tumors have a significant impact on survival rates. Both the ASCO (*56*) and the ESMO (*57*) underscore the importance of basing treatment strategies for initially diagnosed BCLM on the ER, PR, and HER2 status of liver metastatic lesions. They also highlight the necessity of evaluating other treatment-related biomarkers in order to optimize therapeutic approaches. Therefore, evaluating the receptor status of BCLM is of great clinical significance to guiding the formulation of personalized treatment strategies.

The liver is one of the primary targets of distant metastasis in breast cancer cases. Unfortunately, patients with BCLM generally face a rather grim prognosis (*58*). Research by Botteri *et al*. (*15*) has shown that early BCLM patients (within 3 years) who undergo a liver biopsy have higher survival rates than those who do not. Compared to other target organs for distant metastasis of breast cancer, the liver is relatively accessible for biopsy. Thus, a comprehensive and timely assessment of the receptor status and related biomarkers of BCLM according to the latest clinical practice guidelines is crucial to guiding treatment decisions.

In response to changes in the receptor status of BCLM, the latest clinical practice guidelines state that classifying treatment based on molecular subtypes remains the general principle. A point worth highlighting is that nearly one-third of patients with BCLM exhibit a change in HER2 status, changing from no HER2 expression in the primary lesion to low HER2 expression in the liver metastasis. As low HER2-expressing breast cancer targets is researched further, this group of patients will become a potentially targetable population (*59*). Patients with low HER2-expressing BCLM also have new treatment options such as anti-HER2 antibody-drug conjugates (ADCs), and studies on the treatment of low HER2-expressing advanced breast cancer with the HER2 ADC drug T-DXd have become a focus of recent clinical research (*60*).

5. Future prospects

5.1. Molecular mechanisms of receptor heterogeneity in BCLM

In research on the molecular mechanisms of receptor heterogeneity in BCLM, the bidirectional crosstalk between ER and HER2 receptors has been widely reported in the context of endocrine or anti-HER2 treatment resistance in hormone receptor-positive and HER2-positive breast cancer (*61*). Studies have found that ER expression can modulate the activity of the PI3K pathway, thereby influencing the activation of the HER2 pathway. Conversely, HER2 overexpression, often driven by copy number amplification, can lead to the loss of *ER* gene expression. Moreover, multi-omics analysis of metastatic luminal-type primary breast tumors has shown that the transition from the luminal subtype to the HER2-enriched subtype is associated with the expression of ESR1, basal-like molecules, and the activation of related signaling pathways (*62-64*).

Nevertheless, the precise mechanisms driving the changes in receptor status between primary breast cancer and liver metastasis have yet to be fully understood. The precise molecular mechanisms involved in the process of breast cancer liver metastasis need to be explored further, and that effort will lay the foundation for the development of new treatment strategies.

5.2. Research on the reversal of receptor status in BCLM

Schade *et al*. (*65*) examined combined EZH2/AKT inhibitor therapy for triple-negative breast cancer and found that EZH2 and AKT inhibitors induce the expression of GATA3, promoting the transformation of triple-negative breast cancer from a basal-like state to a luminal-like state. Their findings indicate that the receptor status of breast cancer can be reversed under certain conditions, but whether the receptor status of liver metastases can be reversed and whether the specific mechanisms are consistent with those in the primary tumor require further research.

5.3. Artificial intelligence deep learning prediction models for receptor heterogeneity in BCLM

The advent of deep learning has driven the artificial intelligence (AI) revolution, increasing the use of AI in predictive modeling. Today, in relation to breast cancer, many AI models have been developed. For example, Bitencourt *et al*. used magnetic resonance imaging to assess *HER2* gene amplification and predict pathological response after neoadjuvant chemotherapy in HER2-positive breast cancer cases (*66*). Additionally, AI-driven digital pathology has demonstrated effectiveness in tumor diagnosis and treatment.

However, there is still a scarcity of AI models specifically tailored to BCLM. Current guidelines for BCLM typically recommend re-biopsy of liver metastases to re-evaluate their pathological status. Nevertheless, some patients with BCLM cannot tolerate punctures or surgical procedures. This hampers the accurate determination of the receptor status of liver metastases in those patients. Therefore, non-invasive methods of determining the receptor status of BCLM need to be urgently explored. The latest breakthroughs in deep learning technology allow algorithms to learn from clinical data to predict the receptor status of BCLM (*67,68*). On this basis, researchers can train AI models by collecting information on the primary lesion and liver metastasis of patients with BCLM to predict the receptor status of liver metastases and formulate personalized treatment plans based on the predicted receptor status (Figure 1).

5.4. New drug development and clinical evaluation

Considering the liver's pivotal role in detoxification and drug metabolism, a growing number of conventional therapeutics may rapidly lose their efficacy within the liver. Future research should therefore focus on developing new drugs that target molecular markers specific to BCLM, as well as optimizing drug delivery routes to the liver (*69,70*). Additionally, a study has found that a high proportion of ER and PR change from positive to negative in BCLM *(11*), that is, there is a high proportion of conversion from the luminal subtype to the

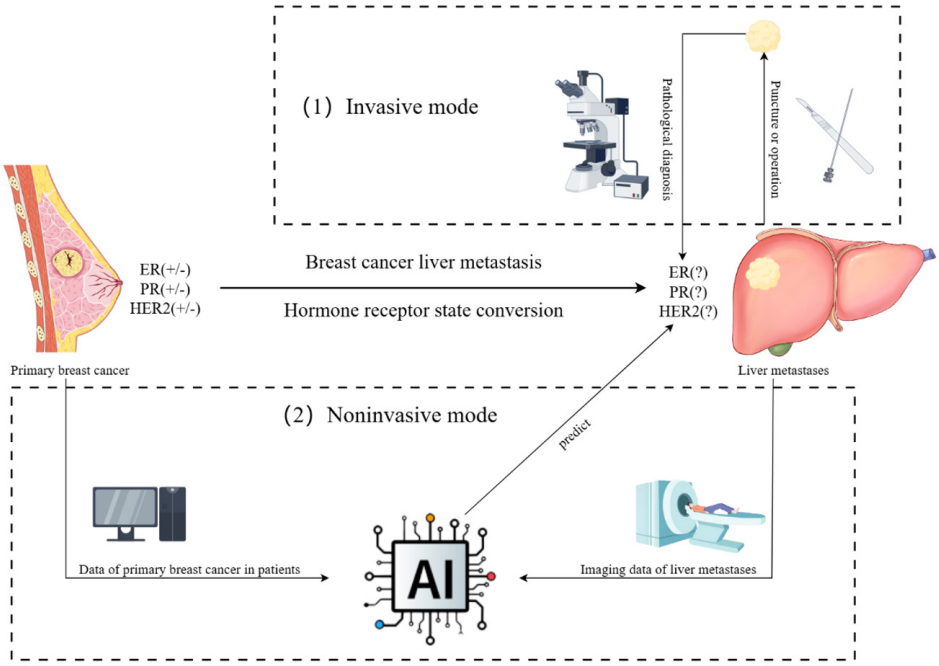

Figure 1. AI-assisted Framework for Predicting Hormone Receptor Status Conversion in Breast Cancer Liver Metastases. This figure illustrates the invasive and noninvasive methods for assessing hormone receptor (HR) status in breast cancer liver metastases. The invasive approach involves biopsy or surgical procedures to obtain pathological diagnoses of estrogen receptor (ER), progesterone receptor (PR), and HER2 status, capturing potential receptor conversions. In contrast, the noninvasive approach uses artificial intelligence to predict HR status changes using data from primary breast cancer and imaging of liver metastases, offering a less invasive alternative for clinical decision-making.

triple-negative subtype, and this has a negative impact on patient prognosis. Therefore, new drugs to reverse the triple-negative subtype of liver metastases to the luminal subtype could be explored and then used to treat those metastases based on ER and PR receptors. This approach has already yielded promising results in the treatment of primary breast cancer (*59*). However, whether it is equally applicable to the treatment of BCLM remains to be determined through large-scale clinical studies.

6. Conclusion

In summary, the changes in receptor status of BCLM represent a complex and pivotal clinical challenge. These changes not only influence the range of treatment options available to patients but also have a direct bearing on prognosis and survival rates. As we gain a better understanding of the molecular mechanisms underlying changes in receptor status and as AI technology is increasingly used in predictive modeling, we can anticipate the development of more precise and targeted treatment strategies.

Future research must concentrate on combination therapies aimed at reversing receptor status, the development of novel drugs, and large-scale clinical studies to assess the tangible impact of treatment modifications on patient survival. These efforts will pave the way for more personalized and effective treatment plans for individuals suffering from BCLM. Ultimately, this will lead to enhanced quality of life and improved survival rates for those patients. With ongoing advances in research, we eagerly anticipate further breakthroughs in the treatment of BCLM. Such progress holds the promise of bringing new hope and better outcomes to patients affected by this condition.

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