Review Article

Analysis of the metastatic mechanism and progress in the treatment of breast cancer liver metastasis: a narrative review

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Background and Objective: Breast cancer is the most common malignancy in women, and metastasis to other target organs is one of the main causes of death. Breast cancer liver metastasis (BCLM) has long been a research focus. Enhancing therapeutic effects, optimizing treatment plans and improving the prognosis of patients are major clinical challenges at present.

Methods: We performed a comprehensive, nonsystematic review of the latest literature to define the current metastatic mechanism and related treatment advances of BCLM.

Key Content and Findings: Due to the lack of research on the mechanism of BCLM, present treatment programs still have limited benefits, and the prognosis of patients is generally poor. New research directions and treatment ideas for BCLM are urgently needed. In this article, we indicated the specific procedures of the BCLM mechanism from the microenvironment to metastasis formation and progress in treatment, including drug therapies such as targeted therapy, surgery, intervention therapy and radiotherapy. Research on the molecular mechanism plays a crucial role in the development of BCLM-related therapies. Based on the metastasis process, we are able to propel new findings and further progression of antineoplastic drugs.

Conclusions: The process of BCLM is multistep, and various factors are involved in it, which provides a powerful theoretical basis for the development of therapeutic methods for treatment of this disease. Further understanding of the mechanism of BCLM is essential to guide clinical management.

Keywords: Breast cancer liver metastasis (BCLM); metastatic mechanism; treatment

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Introduction

The 5-year survival rate for women with metastatic breast cancer (MBC) is only approximately 25%, although it is treatable (1). There are four main target organs of metastasis: bone, lung, liver, and brain. Liver metastasis is usually secondary to lung metastasis in approximately 50% of MBC patients (2). Breast cancer liver metastasis (BCLM), however, has a poor survival rate compared to some other target organs, such as bone and lung metastasis, with an estimated 5-year overall survival (OS) rate of 8.5% (3). The molecular types of tumors reflect different tumor biology, which results in differences in the targets and patterns of the metastasis process. In patients with metastasis, different molecular types can also predict different prognoses (4). One study observed the longest median OS in patients with hormone receptor-positive/human epidermal growth factor receptor 2 (HER2)-positive breast cancer compared to other molecular subtypes, while the shortest OS was observed with the triple-negative breast cancer subtype in patients with BCLM (5).

BCLM can manifest symptoms such as nausea, loss of appetite, and abdominal discomfort. When metastasis damages or destroys the liver structure, pain in the liver area, hepatomegaly, ascites, and jaundice can also appear. There has been relatively more research devoted to the mechanism and treatment of bone and lung metastasis from breast cancer, but less attention has been focused on liver metastasis. Possibly due to differences in metastatic pathways and biological features, BCLM is still considered a systemic disease and is primarily treated with systemic therapy, such as chemotherapy, hormonal therapy, and supportive therapy (6). There are also some specific treatment methods, such as anti-HER2 therapy, bone modifying agents, anti-VEGF therapy, and immune checkpoint inhibitor therapy. Some research has also reported improvements in survival with local treatments, although further studies are required to determine more specific selection criteria for these treatments for BCLM. It is difficult to define the roles of surgery or less-invasive local procedures in the treatment of BCLM. Current treatment programs still confer restricted benefits because of the absence of research on the mechanism of BCLM. Research on its molecular mechanism is important for developing new therapeutics for BCLM. Therefore, understanding the process of breast cancer cell metastasis to the liver and the latest treatment options is crucial. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2463/rc).

Methods

We searched the MEDLINE/PubMed database for relevant literature written in English from 1987 to 2022 using the following search terms: ("breast neoplasms" OR "breast cancer" OR "breast carcinoma") AND ("liver") AND ("neoplasm metastasis" OR "metastasis" OR "metastatic") AND ("mechanism") AND ("therapeutics" OR "treatment" OR "therapy"). Articles appropriate to the topic of this review were fully reviewed. In this article, we summarized the research on the metastatic process of BCLM and current therapeutic methods, which contributed to advancing the clinical study of this disease (*Table 1*).

Discussion

The mechanism of BCLM in vivo

The liver, a blood-rich organ, has diverse molecular targets and a specific tumor microenvironment. Compared with lung and bone, the liver exhibits its own characteristic tumor microenvironment and unique structure, such as a specific hepatic sinusoidal structure, which may be an important factor in the development of BCLM. Although the exact mechanism remains unclear, this is a frontier that is currently being explored (7). The process of BCLM involves multiple steps, and a variety of factors are able to influence it. These include the environmental characteristics of breast cancer itself, the induction of multiple chemokines during metastasis, and the environmental characteristics of the liver itself. The process includes local infiltration of breast cancer cells, infiltration into the circulatory system, migration to the target organ through the circulatory system, exfiltration from the circulatory system, adhesion and colonization of the target organ, and formation of metastatic foci (*Figure 1*). Understanding the concrete steps of the metastasis mechanism provides a strong theoretical foundation for therapeutic methods.

The most widely accepted metastasis model of the mechanism by which tumors migrate to the liver and continue to proliferate was the 'seed and soil' hypothesis proposed by Paget (8). It initially revealed that the formation of metastasis to a secondary organ required the intrinsic properties of tumor cells and a compatible and supportive microenvironment (9). Two other classical

Table 1 Search strategy summary

Item	Specification
Date of search	September 15, 2022 to November 15, 2022
Databases and other sources searched	PubMed/MEDLINE
Search terms used	("breast neoplasms" OR "breast cancer" OR "breast carcinoma") AND ("liver") AND ("neoplasm metastasis" OR "metastasis" OR "metastatic") AND ("mechanism") AND ("therapeutics" OR "treatment" OR "therapy")
Timeframe	1987–2022
Inclusion and exclusion criteria	Inclusion criteria: Original Articles, Review Articles; written in English only Exclusion criteria: Case Reports, Letters to the Editor; non-English language
Selection process	G Liu and F Yang respectively conducted the selection with independence; all authors reviewed the final version of the paper and reached an agreement

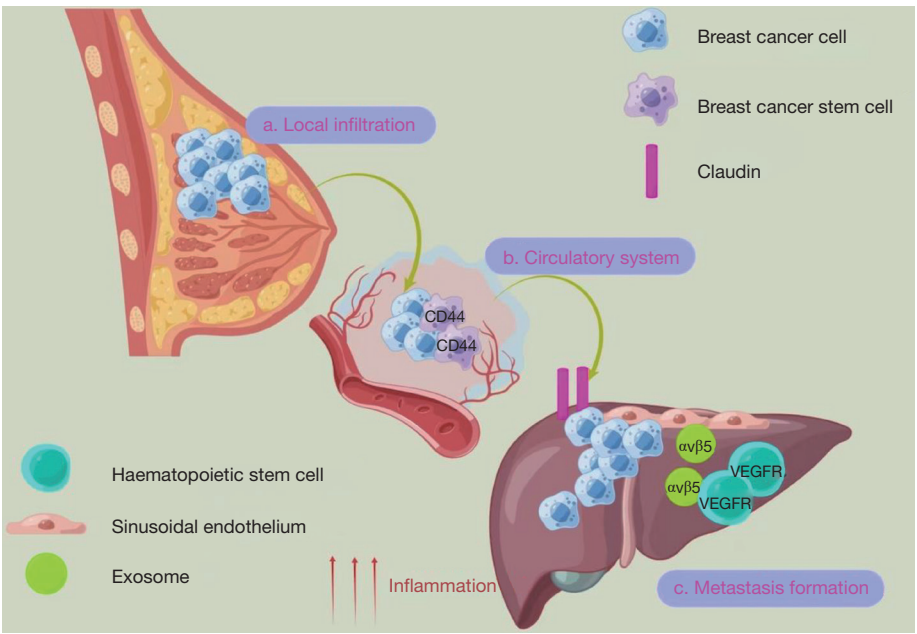

Figure 1 Major process of breast cancer liver metastasis in the microenvironment. a: Cancer cells infiltrate locally in the breast. b: Breast cancer cells and stem cells expressing CD44, which improves metastasis, permeate the circulatory system. c: Breast cancer cells infiltrate the liver tissue from the circulatory system by the key hepatic sinusoidal endothelium structure and transmembrane proteins such as claudin, promoting this process. Various factors, such as VEGFR and exosomes expressing integrin αvβ5, create a microenvironment associated with inflammation and metastasis in the liver. VEGFR, vascular endothelial growth factor receptor.

models of tumor metastasis, the parallel progression model and the linear progression model, were also widely accepted; these two models suggested a similar but not identical view that genetic and nongenetic alterations and selective pressures from the microenvironment led to heterogeneous cell populations and metastatic potential (10).

Generation of the microenvironment

Several factors and cells are involved in tumor progression, including vascular endothelial growth factor receptor (VEGFR), bone marrow-derived haematopoietic progenitor cells (HPCs), and tumor-derived exosomes. Vascular endothelial growth factor (VEGF) is a key player in tumor

neoplasia (11), and breast cancer cells cause haematopoietic stem cells expressing VEGFR to migrate into liver tissue prior to colonization, thus creating a fibronectin-rich microenvironment, which helps circulating breast cancer cells to remain in liver tissue. Kaplan *et al.* (12) showed that removing cells expressing VEGFR from the bone marrow of mice could significantly inhibit the formation of a premetastatic microenvironment, which in turn inhibited metastasis. However, resupplying these cells promoted metastasis. Chien *et al.* (13) found that the inhibition of VEGFR kinase remarkably minimized the formation of liver metastasis and decreased the growth of primary breast cancer. Furthermore, exosomes are related to the metastatic microenvironment as well. Sun *et al.* (14) suggested that exosomes secreted by breast cancer cells first accumulated in liver tissue before liver metastasis occurred and fused with hepatocyte membranes by causing a convergent change in the microenvironment, ultimately producing an environment suitable for the colonization of breast cancer cells. Exosome proteomics shows unique integrin expression profiles, such as integrin αvβ5, which is associated with liver metastasis. During metastatic progression, integrin αvβ5 binds to liver Kupffer cells and contributes to the creation of the premetastatic microenvironment to promote cancer progression. Thus, targeting αvβ5 may reduce the development of BCLM (15).

In this metastatic process, diverse chemokine receptors and their ligands also participate in the formation of the microenvironment. For example, the important chemokine receptor C-X-C chemokine receptor type 4 (CXCR4) promotes metastasis through interaction with its ligand C-X-C chemokine ligand 12 (CXCL12)/stromal cell-derived factor 1α (SDF-1α) (16). In addition, C-C chemokine motif ligand 5 (CCL5) released by tumor cells plays a role in tumor growth (17). Regarding the inflammatory response, tumor necrosis factor-α (TNF-α) induces E-selectin expression in hepatic sinusoidal cells, which is an essential step in generating a proinflammatory microenvironment (10). Goodla *et al.* found that a notably elevated level of the inflammatory factor interleukin 6 (IL-6) was associated with cancer development and progression in patients with liver metastasis (18). Moreover, the inflammatory response itself enhances metastasis (19). For instance, the formation of neutrophil extracellular traps is an important function of neutrophils that can promote breast cancer cells to migrate to the liver.

The formation of metastasis

The sinusoidal endothelium lacking a subendothelial basement membrane can implicate the capability of cancer cells to transmigrate into the liver via blood vessels by controlling liver-specific microvascular exchange and interaction with the microenvironment (20). Tumor cells adhere to the perforated hepatic sinusoidal endothelium from the circulatory system and pass through it into the Disse space to infiltrate the liver tissue, which is the direct route between breast cancer cells and hepatocytes (10). Thus, metastasis occurs.

There are many factors involved in adhesion and colonization as well. Claudin is a crucial transmembrane protein in the tight junction complex, participating in homotypic and heterotypic interactions between adjacent cells (21). Claudin-2, claudin-4, and claudin-7 are essential for the colonization and growth of breast cancer cells in the liver. Among these, claudin-2 facilitates the capability of tumor cells to adhere to other proteins and functional integrin complexes (fibronectin and collagen IV receptors) (22). Currently, it has been shown that in Balb-c mice, the deletion of claudin-4 and claudin-7 improves liver metastasis of breast cancer cells (23). In addition, the high expression of E-cadherin due to loss of methylation increases the adhesion and colonization of breast cancer cells to hepatocytes and boosts the formation of subsequent metastasis, which may be associated with mesenchymal-epithelial transition (MET), considered a marker of increased invasiveness (24). Breast cancer cells with cluster of differentiation-44 (CD44) or cluster of differentiation-24 (CD24) exhibit strong stem cell properties. Cells with high CD44 expression display the characteristics of powerful adhesion, invasiveness, inhibition of apoptosis and promotion of metastasis (25). The stem cell marker CD44, mainly CD44 v5 and v6, can be detected in the serum of breast cancer patients, especially those with liver metastasis, and patients with breast cancer expressing CD44 v6 are more likely to develop liver metastasis (26). This suggests that advanced detection of CD44 expression on breast cancer cells might effectively predict the likelihood of metastasis, which might contribute to the development of targeted therapies.

The vascular system is also likely vital in metastasis. Liang *et al.* (10) demonstrated that metastasis resulted in a nonangiogenic growth pattern in the initial phase, a phase that was not harmful to the organism; in the late phase,

the development of the vascular system at the site of liver metastasis supported breast cancer cells to thrive. During the transition from a nonangiogenic dormant phenotype to an angiogenic phenotype, the expansion of tumor size was connected with the recruitment of endothelial cells from the tumor tissue (27).

Treatment for BCLM

Drug therapy

Chemotherapy

BCLM is currently treated by chemotherapy drugs such as taxanes, anthracyclines, gemcitabine, cisplatin, vinblastine, fluorouracil, etc. In clinical practice, adjuvant and perioperative chemotherapy aim to eradicate early micrometastatic disease, decrease recurrence rates, and improve survival outcomes. Patients with MBC who have not received adjuvant anthracyclines or taxanes in the past should consider them as first-line treatment options (1). However, with their increasing application in the adjuvant treatment of breast cancer, the choices of anthracyclines and taxanes may decrease accordingly after recurrence and metastasis (28). It was recommended to use capecitabine, vinorelbine, or eribulin for breast cancer patients with distant metastases following prior treatment with anthracycline and taxane (29). The CBCSG006 trial demonstrated the status of cisplatin-containing combination regimens in the first-line treatment of MBC (30). The study showed a statistically significant difference of 7.73 [95% CI: 6.46–9.00] months of progression-free survival (PFS) in the cisplatin combined with gemcitabine (GP) group compared with 6.07 [95% CI: 5.32–6.83] months in the paclitaxel combined with gemcitabine (GT) group (P=0.005). In this trial, the status of homologous recombination (HR) deficiency was significantly related to a higher objective response rate (ORR) and longer PFS in the GP group than in the GT group (71.9% *vs.* 38.7%, P=0.008; 10.37 *vs.* 4.30 months, P=0.011). Patients with germ-line BRCA1/2 (gBRCA1/2) mutations had numerically higher ORR and longer PFS in the GP group than in the GT group (83.3% *vs.* 37.5%, P=0.086; 8.90 *vs.* 3.20 months, P=0.459). Germline mutations of BRCA1/2 and the HR panel are potential biomarkers for better performance of cisplatin-based regimens. In addition, a recent study by Park *et al.* (31) showed that for patients with MBC, when combined with gemcitabine, the 6-month PFS rates were 72% (eribulin group) and 73% (paclitaxel group) (P=0.457), and there was no significant difference in OS and PFS between the two groups. The authors suggested that the eribulin group had less neurotoxicity than the paclitaxel group. A recent phase IV study also demonstrated that eribulin was a well-tolerated treatment option in MBC, and its toxicity rarely resulted in treatment discontinuation (32). However, the overall population contained patients with heterogeneous subtypes in the study, and this limited the probability of specific toxicity analysis in biological subtypes, which necessitates further exploration in the future. Hepatic arterial treatment (HAT) combined with chemotherapy has also gradually attracted increasing attention. A study suggested that HAT oxaliplatin in combination with capecitabine for liver metastases in patients with MBC had high response rates of 42.3% (95% CI: 28.7–56.8%) and a long median PFS of 10.8 months (95% CI: 6.9–14.7 months) and OS of 27.6 months (95% CI: 20.4–34.8 months) (33). Furthermore, when combined with atezolizumab, chemotherapy treatment yielded a clinically meaningful OS benefit in patients with related immune biomarker cell-positive metastatic triple-negative breast cancer and might be a significant therapeutic choice (34).

In terms of the duration of systemic chemotherapy, most expert recommendations indicated continuation of effective treatment until disease progression or unacceptable toxicity. In actual clinical work, special attention should be given to the impact of treatment on the patient's general condition and quality of life, and a balance between efficacy and quality of life should be pursued.

Endocrine therapy

Commonly used first-line endocrine therapy includes selective estrogen receptor modulators (tamoxifen), selective estrogen receptor downregulators (fulvestrant), or third-generation aromatization enzyme inhibitors for postmenopausal patients (anastrozole, letrozole, exemestane).

The Society of Medical Oncology recommended that endocrine therapy should be the preferred treatment for patients with hormone receptor-positive advanced breast cancer (ABC) with or without visceral metastasis unless there was evidence of visceral crisis or clear endocrine resistance (1). Endocrine drug resistance is a major barrier to current endocrine therapy. The mechanism of endocrine drug resistance in breast cancer is not yet clear, but some studies have found that changes in the phosphatidylinositol-3-kinase (PI3K) signaling pathway are related to resistance (35-38). In the phase III SOLAR-1 randomized study, the PI3K inhibitor alpelisib combined with fulvestrant

increased median PFS by approximately 5 months in postmenopausal women with hormone receptor-positive, HER2-negative, PIK3CA-mutated MBC, which is a crucial breakthrough in the history of endocrine therapy (39). This trial also indicated that the median OS (95% CI) in patients with BCLM was 37.2 months (28.7–43.6 months) and 22.8 months (19.0–26.8 months) in the alpelisib-fulvestrant and placebo-fulvestrant arms, respectively [HR =0.68 (0.46–1.00)] (40). The combination of endocrine therapy with other treatments was also reported by Schettini *et al.* (41). They suggested that endocrine therapy with cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, as first- or second-line treatments, might prolong PFS for patients with hormone receptor-positive/HER2-negative MBC. The combination may also improve OS compared to endocrine therapy alone (41). In addition, although CDK4/6 inhibitors have shown clinical efficacy in patients with estrogen receptor-positive MBC, estrogen receptor-positive breast cancer cells can rapidly adapt to CDK4/6 inhibition and escape cytostatic inhibition, resulting in primary and acquired drug resistance: combination therapy can also successfully prevent this (42).

Targeted therapy

Breast cancer cells in the liver thrive in a microenvironment characterized by the absence of a subendothelial basement membrane and fenestrated endothelium in sinusoidal capillaries (43). The binding of VEGFs to the VEGFR1-3 receptors activates the VEGF signaling pathway in endothelial cells (44). Therefore, the inhibition of VEGFR kinases decreased metastasis to the liver. Bevacizumab, a humanized monoclonal antibody that binds to all circulating VEGF-A isoforms, was the first antiangiogenic therapy available. There was a report of a woman with a BRCA2 germline mutation who was successfully treated with a combination of bevacizumab/paclitaxel/carboplatin (BPC). Despite liver metastases and pregnancy, the patient maintained a complete clinical response for approximately five years (45). This finding suggested that blocking VEGF pathways with drugs such as bevacizumab could be considered a good treatment option for MBC.

HER2 is a transmembrane tyrosine kinase protein belonging to the human epidermal growth factor receptor (EGFR) family of proteins. HER2 amplification and overexpression are associated with aggressive tumor biology and poorer prognosis (46). Several anti-HER2 agents have been developed for clinical use, including monoclonal antibodies (trastuzumab, pertuzumab), small molecule tyrosine kinase inhibitors (lapatinib, neratinib), and antibody-drug conjugates (T-DM1). Ji *et al.* (5) found that compared to the hormone receptor-positive/HER2-negative subgroup, the hormone receptor-positive/HER2-positive subgroup had a significantly lower risk of death (HR =0.74; 95% CI: 0.58–0.95; P<0.001) for patients receiving HER2-targeted therapy. A phase III randomized clinical study indicated that for patients with hormone receptor-positive and HER2-positive MBC subgroups, in contrast to the single targeted drug (lapatinib/trastuzumab) combined with aromatase inhibitor therapy, the PFS was significantly prolonged when these two targeted drugs were combined with aromatase inhibitor therapy (47). This combination provides an effective and safe alternative treatment option to chemotherapy for this patient population subgroup. Moreover, studies on single-agent *vs.* double-agent chemotherapy combined with trastuzumab for the treatment of HER2-positive MBC had mixed results (48). To resolve this contradiction, a meta-analysis by Yu *et al.* (49) showed that the PFS and OS of patients with HER2-positive MBC treated with dual-drug chemotherapy combined with trastuzumab were better, but the treatment-related toxicity was more severe. BCLM can cause liver function damage, so the scope of application of dual-drug chemotherapy combined with trastuzumab needs to be explored in relevant clinical trials. A recent study by Xie *et al.* (50) indicated that pyrotinib plus trastuzumab and a single chemotherapeutic agent offered a promising choice with a manageable safety profile for patients with heavily pretreated HER2-positive MBC with a median PFS of 7.5 months (95% CI: 4.7 to 9.9 months) and ORR of 50.5% (20/40). However, to further confirm the efficacy and safety of this combination regimen, multicenter randomized controlled trials in larger populations are needed.

Surgery

Although BCLM can be treated with systemic therapies such as chemotherapy, antiangiogenic therapy, and targeted therapy, the prognosis remains poor (51). Therefore, other types of effective treatments, including local treatments such as surgery, are urgently needed. However, contrary to the substantial evidence for treating colorectal liver metastases locally, there are limited data on the resection of BCLM.

Growing evidence suggests that liver resection improves 5- or 10-year survival after BCLM surgery (52). He *et al.* (53) showed that the 5-year OS of the BCLM patient cohort was as high as 32.2%, and the median survival time was

57.59 months, which both indicated that surgery was an important management strategy in improving the prognosis of selected patients. A limited number of BCLM patients are eligible for surgery because of the extent and location of the disease and physical condition. For patients who have undergone liver surgery, primary tumor characteristics, such as small tumor size, low-grade tumor, node negativity, and early stage, might indicate a better prognosis, as demonstrated by a recent review (54). However, it is controversial whether radical or nonradical resection results in a better outcome. Elias *et al.* (55) showed that the median survival after R0 or R1/R2 resection was 40 and 31 months, respectively, without a significant difference. Nevertheless, Orlandi *et al.* (56) found that in a retrospective analysis, negative resection margin (R0) was the only factor that significantly enhanced OS compared to positive resection margin [78 *vs.* 16 months; HR 0.083, 95% CI (not mentioned), P<0.0001] and disease-free interval (DFI) [16 *vs.* 5 months; HR 0.17, 95% CI (not mentioned), P=0.0058]. Presently, there is no consensus on the specific method for liver resection. A retrospective study focused on performing anatomical resection (standard liver lobectomy, liver segment resection) or nonanatomical resection (wedge resection, excavation, etc.), but there was no evidence to support the difference in survival between the two groups (57).

Moreover, regarding the prognostic factor related to hormone receptors, there is a study pointing out that their status was not associated with postoperative outcome (52). Abbott *et al.* (58) and Elias *et al.* (55) reported a negative impact of hormone receptor deficiency on disease-free survival (DFS), but only in a univariate analysis. Complications were seldom described (including type and grade) in the literature. Only Abbott *et al.* (58) and Adam *et al.* (59) detailed the ratio between minor events (15–19%) and major events (5%). Furthermore, in the retrospective analysis by Orlandi *et al.* (56), surgical complications occurred in only two patients, and their data suggested that liver metastasis resection might be a safe procedure. In summary, based on most studies, almost no life-threatening complications were noted in patients with BCLM who had undergone surgery (60-62). Due to its invasiveness, surgical resection of BCLM is still controversial despite some promising reports. Liver recurrences and extrahepatic recurrences were diagnosed at a mean interval of 15 months and 22 months after hepatectomy (63).

Intervention therapy

Intervention therapy, a local treatment including ablation and transcatheter arterial chemoembolization (TACE), is attempted for patients at high surgical risk and shows positive results. Radiofrequency ablation (RFA) includes three main approaches: ultrasound-guided percutaneous RFA, laparoscopic RFA and intraoperative RFA. The standard RFA technique can elevate the temperature of local tissue beyond 100 ℃, causing coagulative necrosis of the tumor tissue and surrounding liver parenchyma. Meanwhile, the vascular tissue around the tumor forms a reaction zone, which prevents continued blood supply. The necrosis rate after RFA for BCLM exceeds 90% (64), comparable to the necrosis rate observed in the literature for colorectal liver metastasis (CRLM) or hepatocellular carcinoma, and this technique has a low incidence of postoperative complications. Even so, it is still contested whether the technique offers good efficacy for surgically unresectable primary or metastatic hepatic tumors. Some small-scale prospective studies of breast cancer patients with 1 to 3 liver metastases proposed that RFA was effective in 75% to 92% of patients, and the 1-year survival rate was 64% to 95% (54,65,66). However, according to another study, patients with BCLM >2.5 cm have significantly reduced survival after RFA (67). Meloni *et al.* (68) reported their experience with RFA (n=52), describing a 5-year survival rate of 27% and finding worse OS in patients with lesions >2.5 cm. More generally, the literature reviews presented by Taşçi *et al.* and Vogl *et al.* (69,70) concluded that post-RFA OS for BCLM was between 10 and 60 months, with recurrence rates between 13% and 58%, especially for patients with larger lesions. Microwave ablation (MWA) is another important ablation strategy with greater and more rapid thermal energy transfer (71). It has a more effective local control ability than RFA (100% coverage of metastatic lesions *vs.* 85–97%), with a median survival time of 32 months and a local progression rate of 9.6% (72-74). In addition, the recurrence rate of MWA is also relatively low, at approximately 10% (70). With regard to TACE, a recent development was that Chang *et al.* (6) discovered drug-eluting beads for transarterial chemoembolization (DEB-TACE), a novel drug delivery system using microspheres as embolic agents to load chemotherapeutic drugs for the treatment of BCLM. DEB-TACE is characterized by

minimal trauma, a low rate of complications, and is safe and effective. This approach has been applied in clinical practice, with higher intratumoral concentrations and lower systemic drug concentrations than conventional TACE.

Radiotherapy

Bale *et al.* (54) suggested that there were three main types of treatment for BCLM: selective internal radiation therapy (SIRT) mainly for palliative care, stereotactic body radiation therapy (SBRT), and interstitial brachytherapy (BT). SIRT is still being evaluated in many pathologies, and its status remains to be determined. The indication of SIRT for BCLM patients based on studies is unresectable or progressive disease with systemic chemotherapy (52). Unlike conventional radiation therapy, SIRT delivers high-dose radiation selectively to targeted lesions and minimizes collateral damage to normal liver tissue (75). It is based on the administration of yttrium-90 (90 Y) microspheres with a diameter of approximately 30 μm via the arterial blood supply of liver tumors (54). A study showed that 58 patients with BCLM treated with SIRT had a median OS of 47 weeks (76). However, exact figures are still not identical due to a lack of extensive research. A report showed that adverse events of SIRT included radioembolization-induced liver disease (REILD), postradioembolization syndrome (PRS), biliary complications, radiation pneumonitis, gastroduodenal ulceration, lymphopenia, vascular injury, and portal hypertension (77). Onal *et al.* (78) retrospectively analyzed patients with BCLM receiving SBRT. The 1- and 2-year OS rates were 85% and 57%, respectively, and the 1- and 2-year local control rates were 100% and 88%, respectively. None of the treated patients developed grade 4 or 5 treatment-related toxicity. Another study from 25 centers considered that patients with BCLM treated with SBRT had an OS of 21 months, and they found that BED10 (with dose fractionations normalized to BED10) ≥100 Gy improved OS (79). Based on the reports, we supposed that SBRT was an effective option for patients with BCLM with good local control and promising survival rates, which was also consistent with the study by Oymak *et al.* (80). The selection criteria for patients with SBRT and the optimal dose for the liver are being studied. CT-guided BT is a safe and effective treatment, but further research is still needed because of the absence of data.

Conclusions

This article demonstrated the major mechanisms related to metastasis and the currently available treatment options in the management of BCLM. The process of BCLM is multistep, and there may be other factors affecting the metastasis process and potential mechanisms waiting to be explored further. At present, the survival of patients with BCLM is not promising. Due to the unique characteristics (especially tumor phenotype) of every BCLM patient, each treatment plan should take into account age, patient general status, hormonal status, HER2 overexpression, number and location of metastases, absence of disease interval and other personalized parameters. However, because of the lack of clinical data, there are still no specific standard-of-care therapeutic strategies indicated for patients with BCLM. Research on the mechanism of BCLM has promoted the development of treatments for this disease and provided an inspiring theoretical basis. The choice of a more efficacious management strategy to improve the prognosis of patients needs to be probed in the future.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). Ann Oncol 2018;29:1634-57.
2. He ZY, Wu SG, Peng F, et al. Up-Regulation of RFC3 Promotes Triple Negative Breast Cancer Metastasis and is Associated With Poor Prognosis Via EMT. Transl Oncol 2017;10:1-9.
3. Pentheroudakis G, Fountzilas G, Bafaloukos D, et al. Metastatic breast cancer with liver metastases: a registry analysis of clinicopathologic, management and outcome characteristics of 500 women. Breast Cancer Res Treat 2006;97:237-44.
4. Gao D, Du J, Cong L, et al. Risk factors for initial lung metastasis from breast invasive ductal carcinoma in stages I-III of operable patients. Jpn J Clin Oncol 2009;39:97-104.
5. Ji L, Cheng L, Zhu X, et al. Risk and prognostic factors of breast cancer with liver metastases. BMC Cancer 2021;21:238.
6. Chang X, Sun P, Zhang J, et al. CalliSpheres drug-eluting beads transarterial-chemoembolization in the treatment of liver metastases from breast cancer: Initial experience in 14 patients. Medicine (Baltimore) 2021;100:e28407.
7. Jiang H, Yu D, Yang P, et al. Revealing the transcriptional heterogeneity of organ-specific metastasis in human gastric cancer using single-cell RNA Sequencing. Clin Transl Med 2022;12:e730.
8. Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer 2003;3:453-8.
9. Jost T, Heinzerling L, Fietkau R, et al. Palbociclib Induces Senescence in Melanoma and Breast Cancer Cells and Leads to Additive Growth Arrest in Combination With Irradiation. Front Oncol 2021;11:740002.
10. Liang Y, Zhang H, Song X, et al. Metastatic heterogeneity of breast cancer: Molecular mechanism and potential therapeutic targets. Semin Cancer Biol 2020;60:14-27.
11. Nash AD, Baca M, Wright C, et al. The biology of vascular endothelial growth factor-B (VEGF-B). Pulm Pharmacol Ther 2006;19:61-9.
12. Kaplan RN, Riba RD, Zacharoulis S, et al. VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. Nature 2005;438:820-7.
13. Chien MH, Lee LM, Hsiao M, et al. Inhibition of Metastatic Potential in Breast Carcinoma In Vivo and In Vitro through Targeting VEGFRs and FGFRs. Evid Based Complement Alternat Med 2013;2013:718380.
14. Sun F, Wang JZ, Luo JJ, et al. Exosomes in the Oncobiology, Diagnosis, and Therapy of Hepatic Carcinoma: A New Player of an Old Game. Biomed Res Int 2018;2018:2747461.
15. Hoshino A, Costa-Silva B, Shen TL, et al. Tumour exosome integrins determine organotropic metastasis. Nature 2015;527:329-35.
16. Müller A, Homey B, Soto H, et al. Involvement of chemokine receptors in breast cancer metastasis. Nature 2001;410:50-6.
17. Soria G, Ben-Baruch A. The inflammatory chemokines CCL2 and CCL5 in breast cancer. Cancer Lett 2008;267:271-85.
18. Goodla L, Xue X. The Role of Inflammatory Mediators in Colorectal Cancer Hepatic Metastasis. Cells 2022;11:2313.
19. Auguste P, Fallavollita L, Wang N, et al. The host inflammatory response promotes liver metastasis by increasing tumor cell arrest and extravasation. Am J Pathol 2007;170:1781-92.
20. Reichen J. The Role of the Sinusoidal Endothelium in Liver Function. News Physiol Sci 1999;14:117-21.
21. Turksen K, Troy TC. Barriers built on claudins. J Cell Sci 2004;117:2435-47.
22. Tabariès S, Dong Z, Annis MG, et al. Claudin-2 is selectively enriched in and promotes the formation of breast cancer liver metastases through engagement of integrin complexes. Oncogene 2011;30:1318-28.
23. Erin N, Wang N, Xin P, et al. Altered gene expression

in breast cancer liver metastases. Int J Cancer 2009;124:1503-16.
24. Chao Y, Wu Q, Shepard C, et al. Hepatocyte induced re-expression of E-cadherin in breast and prostate cancer cells increases chemoresistance. Clin Exp Metastasis 2012;29:39-50.
25. Zöller M. CD44: can a cancer-initiating cell profit from an abundantly expressed molecule? Nat Rev Cancer 2011;11:254-67.
26. Sun H, Jia J, Wang X, et al. CD44+/CD24- breast cancer cells isolated from MCF-7 cultures exhibit enhanced angiogenic properties. Clin Transl Oncol 2013;15:46-54.
27. Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell 1996;86:353-64.
28. Bines J, Earl H, Buzaid AC, et al. Anthracyclines and taxanes in the neo/adjuvant treatment of breast cancer: does the sequence matter? Ann Oncol 2014;25:1079-85.
29. Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). Ann Oncol 2017;28:3111.
30. Zhang J, Lin Y, Sun XJ, et al. Biomarker assessment of the CBCSG006 trial: a randomized phase III trial of cisplatin plus gemcitabine compared with paclitaxel plus gemcitabine as first-line therapy for patients with metastatic triple-negative breast cancer. Ann Oncol 2018;29:1741-7.
31. Park YH, Im SA, Kim SB, et al. Phase II, multicentre, randomised trial of eribulin plus gemcitabine versus paclitaxel plus gemcitabine as first-line chemotherapy in patients with HER2-negative metastatic breast cancer. Eur J Cancer 2017;86:385-93.
32. La Verde N, Damia G, Garrone O, et al. Tolerability of Eribulin and correlation between polymorphisms and neuropathy in an unselected population of female patients with metastatic breast cancer: results of the multicenter, single arm, phase IV PAINTER study. Breast Cancer Res 2022;24:71.
33. Lindgaard SC, Brinch CM, Jensen BK, et al. Hepatic arterial therapy with oxaliplatin and systemic capecitabine for patients with liver metastases from breast cancer. Breast 2019;43:113-9.
34. Schmid P, Rugo HS, Adams S, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2020;21:44-59.
35. Paplomata E, O'Regan R. The PI3K/AKT/mTOR pathway in breast cancer: targets, trials and biomarkers. Ther Adv Med Oncol 2014;6:154-66.
36. Guerrero-Zotano A, Mayer IA, Arteaga CL. PI3K/AKT/mTOR: role in breast cancer progression, drug resistance, and treatment. Cancer Metastasis Rev 2016;35:515-24.
37. Miller TW, Balko JM, Arteaga CL. Phosphatidylinositol 3-kinase and antiestrogen resistance in breast cancer. J Clin Oncol 2011;29:4452-61.
38. Nunnery SE, Mayer IA. Targeting the PI3K/AKT/mTOR Pathway in Hormone-Positive Breast Cancer. Drugs 2020;80:1685-97.
39. Büyükkaramikli NC, de Groot S, Riemsma R, et al. Ribociclib with an Aromatase Inhibitor for Previously Untreated, HR-Positive, HER2-Negative, Locally Advanced or Metastatic Breast Cancer: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. Pharmacoeconomics 2019;37:141-53.
40. André F, Ciruelos EM, Juric D, et al. Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: final overall survival results from SOLAR-1. Ann Oncol 2021;32:208-17.
41. Schettini F, Giudici F, Giuliano M, et al. Overall Survival of CDK4/6-Inhibitor-Based Treatments in Clinically Relevant Subgroups of Metastatic Breast Cancer: Systematic Review and Meta-Analysis. J Natl Cancer Inst 2020;112:1089-97.
42. Correction: Early Adaptation and Acquired Resistance to CDK4/6 Inhibition in Estrogen Receptor-Positive Breast Cancer. Cancer Res 2016;76:5907.
43. Katoh M. FGFR inhibitors: Effects on cancer cells, tumor microenvironment and whole-body homeostasis (Review). Int J Mol Med 2016;38:3-15.
44. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med 2003;9:669-76.
45. Ogata H, Kikuchi Y, Natori K, et al. Liver Metastasis of a Triple-Negative Breast Cancer and Complete Remission for 5 Years After Treatment With Combined Bevacizumab/Paclitaxel/Carboplatin: Case Report and Review of the Literature. Medicine (Baltimore) 2015;94:e1756.
46. Ross JS, Slodkowska EA, Symmans WF, et al. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist 2009;14:320-68.
47. Johnston SRD, Hegg R, Im SA, et al. Phase III, Randomized Study of Dual Human Epidermal Growth Factor Receptor 2 (HER2) Blockade With Lapatinib

Plus Trastuzumab in Combination With an Aromatase Inhibitor in Postmenopausal Women With HER2-Positive, Hormone Receptor-Positive Metastatic Breast Cancer: Updated Results of ALTERNATIVE. J Clin Oncol 2021;39:79-89.
48. Robert N, Leyland-Jones B, Asmar L, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. J Clin Oncol 2006;24:2786-92.
49. Yu YF, Wang Y, Fu TP, et al. Trastuzumab combined with doublet or single-agent chemotherapy as first-line therapy for HER2-positive metastatic breast cancer. Breast Cancer Res Treat 2018;168:337-48.
50. Xie XF, Zhang QY, Huang JY, et al. Pyrotinib combined with trastuzumab and chemotherapy for the treatment of human epidermal growth factor receptor 2-positive metastatic breast cancer: a single-arm exploratory phase II trial. Breast Cancer Res Treat 2023;197:93-101.
51. Zinser JW, Hortobagyi GN, Buzdar AU, et al. Clinical course of breast cancer patients with liver metastases. J Clin Oncol 1987;5:773-82.
52. Golse N, Adam R. Liver Metastases From Breast Cancer: What Role for Surgery? Indications and Results. Clin Breast Cancer 2017;17:256-65.
53. He X, Zhang Q, Feng Y, et al. Resection of liver metastases from breast cancer: a multicentre analysis. Clin Transl Oncol 2020;22:512-21.
54. Bale R, Putzer D, Schullian P. Local Treatment of Breast Cancer Liver Metastasis. Cancers (Basel) 2019;11:1341.
55. Elias D, Maisonnette F, Druet-Cabanac M, et al. An attempt to clarify indications for hepatectomy for liver metastases from breast cancer. Am J Surg 2003;185:158-64.
56. Orlandi A, Pontolillo L, Mele C, et al. Liver Metastasectomy for Metastatic Breast Cancer Patients: A Single Institution Retrospective Analysis. J Pers Med 2021;11:187.
57. Boudreaux JP, Klimstra DS, Hassan MM, et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the Jejunum, Ileum, Appendix, and Cecum. Pancreas 2010;39:753-66.
58. Abbott DE, Brouquet A, Mittendorf EA, et al. Resection of liver metastases from breast cancer: estrogen receptor status and response to chemotherapy before metastasectomy define outcome. Surgery 2012;151:710-6.
59. Adam R, Aloia T, Krissat J, et al. Is liver resection justified for patients with hepatic metastases from breast cancer? Ann Surg 2006;244:897-907; discussion 907-8.
60. Ruiz A, Castro-Benitez C, Sebagh M, et al. Repeat Hepatectomy for Breast Cancer Liver Metastases. Ann Surg Oncol 2015;22 Suppl 3:S1057-66.
61. Kostov DV, Kobakov GL, Yankov DV. Prognostic factors related to surgical outcome of liver metastases of breast cancer. J Breast Cancer 2013;16:184-92.
62. Selzner M, Morse MA, Vredenburgh JJ, et al. Liver metastases from breast cancer: long-term survival after curative resection. Surgery 2000;127:383-9.
63. Lermite E, Marzano E, Chéreau E, et al. Surgical resection of liver metastases from breast cancer. Surg Oncol 2010;19:e79-84.
64. Livraghi T, Goldberg SN, Solbiati L, et al. Percutaneous radio-frequency ablation of liver metastases from breast cancer: initial experience in 24 patients. Radiology 2001;220:145-9.
65. Rivera K, Jeyarajah DR, Washington K. Hepatectomy, RFA, and Other Liver Directed Therapies for Treatment of Breast Cancer Liver Metastasis: A Systematic Review. Front Oncol 2021;11:643383.
66. Bai XM, Yang W, Zhang ZY, et al. Long-term outcomes and prognostic analysis of percutaneous radiofrequency ablation in liver metastasis from breast cancer. Int J Hyperthermia 2019;35:183-93.
67. Chen MH, Wei Y, Yan K, et al. Treatment strategy to optimize radiofrequency ablation for liver malignancies. J Vasc Interv Radiol 2006;17:671-83.
68. Meloni MF, Andreano A, Laeseke PF, et al. Breast cancer liver metastases: US-guided percutaneous radiofrequency ablation--intermediate and long-term survival rates. Radiology 2009;253:861-9.
69. Taşçi Y, Aksoy E, Taşkın HE, et al. A comparison of laparoscopic radiofrequency ablation versus systemic therapy alone in the treatment of breast cancer metastasis to the liver. HPB (Oxford) 2013;15:789-93.
70. Vogl TJ, Farshid P, Naguib NN, et al. Thermal ablation therapies in patients with breast cancer liver metastases: a review. Eur Radiol 2013;23:797-804.
71. Poulou LS, Botsa E, Thanou I, et al. Percutaneous microwave ablation vs radiofrequency ablation in the treatment of hepatocellular carcinoma. World J Hepatol 2015;7:1054-63.
72. Lorentzen T, Skjoldbye BO, Nolsoe CP. Microwave ablation of liver metastases guided by contrast-enhanced ultrasound: experience with 125 metastases in 39 patients. Ultraschall Med 2011;32:492-6.
73. Abe H, Kurumi Y, Naka S, et al. Open-configuration

MR-guided microwave thermocoagulation therapy for metastatic liver tumors from breast cancer. Breast Cancer 2005;12:26-31.
74. Iannitti DA, Martin RC, Simon CJ, et al. Hepatic tumor ablation with clustered microwave antennae: the US Phase II trial. HPB (Oxford) 2007;9:120-4.
75. Kennedy A, Coldwell D, Sangro B, et al. Radioembolization for the treatment of liver tumors general principles. Am J Clin Oncol 2012;35:91-9.
76. Haug AR, Tiega Donfack BP, Trumm C, et al. 18F-FDG PET/CT predicts survival after radioembolization of hepatic metastases from breast cancer. J Nucl Med 2012;53:371-7.
77. Riaz A, Lewandowski RJ, Kulik LM, et al. Complications following radioembolization with yttrium-90 microspheres: a comprehensive literature review. J Vasc Interv Radiol 2009;20:1121-30; quiz 1131.
78. Onal C, Guler OC, Yildirim BA. Treatment outcomes of breast cancer liver metastasis treated with stereotactic body radiotherapy. Breast 2018;42:150-6.
79. Mahadevan A, Blanck O, Lanciano R, et al. Stereotactic Body Radiotherapy (SBRT) for liver metastasis - clinical outcomes from the international multi-institutional RSSearch® Patient Registry. Radiat Oncol 2018;13:26.
80. Oymak E, Guler OC, Onal C. Significance of liver metastasis volume in breast cancer patients treated with stereotactic body radiotherapy. Strahlenther Onkol 2022;198:247-53.

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