Peer Review File

Article Information: https://dx.doi.org/10.21037/tcr-22-2463

Review Comments (Round 1)

Reviewer A

Major point

Comment 1: You should not describe the metastatic mechanism and clinical data independently in one paper. If you would like to discuss basic study and clinical outcome simultaneously, you should correlate them. Your review about clinical trials needs extensive revision.

Reply 1: Many thanks to the reviewer for giving us valuable suggestions. The liver has a unique tumor microenvironment and structure that may contribute to BCLM development. Many factors can affect the BCLM process, which includes multiple steps. Therefore, understanding the specific mechanism of BCLM may impede metastasis and contribute to the development of related treatments, especially some drugs. We have modified our text as advised (see Page 3, line 52-54 and Page 4, line 82-84). Relevant content is marked in red in the revised manuscript.

Changes in the text:

1.Current treatment programs still have restricted benefits, because of the absence of research on the mechanism of BCLM. Research on its molecular mechanism is of importance to developing new therapeutics for BCLM.

2.Understanding the concrete steps of the metastasis mechanism provides a strong theoretical foundation for therapeutic methods.

Comment 2: Why does your paper lack Results section?

Reply 2: Many thanks to the reviewer's comment.We are really sorry that we may not understand the reviewer's comment. We have written the Summary section in the article as required.

Minor points

Comment 1: Line 27

The expression “despite the advances in treatment strategies” should be revised.

Reply 1: We have modified our text as advised (see Page 2, line 27).

Changes in the text: although treatable

Comment 2: Line 30

The expression “locality recurrence” should be revised.

Reply 2: We have modified our text as advised (see Page 2, line 30-31).

Changes in the text: some other target organs such as bone and lung metastasis

Comment 3: Line 33

The expression “metastasis spread” should be revised.

Reply 3: We have modified our text as advised (see Page 2, line 33).

Changes in the text: metastasis process

Comment 4: Line 46

You’d should mention anti-HER2 therapy, bone modifying agents, anti-VEGEF therapy, and immune check point inhibitory therapy.

Reply 4: We have modified our text as advised (see Page 3, line 46-48).

Changes in the text: There are also some specific treatment methods like anti-HER2 therapy, bone modifying agents, anti-VEGEF therapy, and immune check point inhibitory therapy.

Comment 5: Line 82

leaded → led

Reply 5: We have modified our text as advised (see Page 5, line 92).

Changes in the text: led

Comment 6: Line 114

The expression “several literature reports” spoiled be revised.

Reply 6: We have modified our text as advised (see Page 6, line 124-126).

Changes in the text: And Goodla et al. found that the notably elevated level of the inflammatory factor interleukin 6 (IL-6) was associated with cancer development and progression in patients with liver metastasis (18).

Comment 7: Line 124

The expression “outside circulatory system” should be revised.

Reply 7: We have modified our text as advised (see Page 6, line 135).

Changes in the text: the circulatory system

Comment 8: Line 146

The expression “target preventive therapies” is strange.

Reply 8: We have modified our text as advised (see Page 7, line 157).

Changes in the text: this might contribute to the development of target therapies

Comment 9: Lines 157-8

"Single chemotherapy" and "combined chemotherapy regimens" should be revised.

You should list the word "taxanes" first among various anticancer agents.

Reply 9: We have modified our text as advised (see Page 8, line 168).

Changes in the text: taxanes,

Comment 10: Lines 158-61

This sentence is not true. You should study the BCLM chemotherapy.

Reply 10: We have modified our text as advised (see Page 8, line 169-171).

Changes in the text: adjuvant and perioperative chemotherapy aim to eradicate early micrometastatic disease, decrease recurrence rates, and improve survival outcomes.

Comment 11: Line 196

You should use the abbreviation of ABC after full spelling.

Reply 11: We have used "advanced breast cancer (ABC)" on Page 10, line 200-201 before.

Comment 12: Lines 199-200

What's the meaning of"first- or second-line treatment for the prognosis of hormone receptor-positive / HER2-negative metastatic breast cancer"?

Reply 12: This is a study background of a systematic review and meta-analysis, which searched to select all available phase II or III randomized clinical trials of CDK4/6 inhibitors with endocrine therapy reporting OS data in first- or second-line therapy of HR+/HER2-negative pre- or postmenopausal metastatic breast cancer.

Comment 13: Line 202

What's the meaning of "CDK4/6 alone inhibitors"?

Reply 13: We have modified our text as advised (see Page 10, line 215).

Changes in the text: CDK4/6 inhibitors

Comment 14: Lines 203-4

You should revise the expression " breast cancer cells can rapidly adapt to CDK4/6 inhibition".

Reply 14: We have modified our text as advised (see Page 10, line 216-217).

Changes in the text: breast cancer cells can adapt to CDK4/6 inhibition at a quick speed

Comment 15: Lines 260-1

You should revise the sentence “almost no patients with BCLM who have experienced resection tend to appear death related to operations itself and postoperative complications”.

Reply 15: We have modified our text as advised (see Page 13, line 277-278).

Changes in the text: almost no life-threatening complications were noted in patients with BCLM who have experienced the operations

Comment 16: Lines 266-8

You should revise the sentence “There are three approaches for radiofrequency ablation (RFA), ultrasound-guided percutaneous radiofrequency ablation, laparoscopic radiofrequency ablation and intraoperative radiofrequency ablation” properly.

Reply 16: We have modified our text as advised (see Page 14, line 286-288).

Changes in the text: Radiofrequency ablation (RFA) includes three main approaches, ultrasound-guided percutaneous radiofrequency ablation, laparoscopic radiofrequency ablation and intraoperative radiofrequency ablation.

Reviewer B

The manuscript submitted by the authors well describes the comprehensive mechanism and treatment of breast cancer liver metastasis through narrative review but still has some problems as indicated below.

Comment 1: The discussion of drug-therapy for BCLM should focus on the systemic therapy specifically based on the liver metastasis. It is not much important to generally describe the systemic therapy for breast cancer, considering the aim of this paper.

Reply 1: Many thanks to the reviewer for giving us valuable suggestions.We have shown the chemotherapy, endocrine therapy and targeted therapy of metastatic breast cancer in the article, due to the lack of research on the development of specific drugs for the liver metastasis. What’s more, The Guidelines of the European Society of Internal Oncology suggest that endocrine therapy should be the first choice for patients with hormone receptor positive regardless of whether there is visceral metastasis, except for visceral crisis or clear evidence of endocrine drug resistance.We searched the relevant literature again and supplemented the research on the development of drugs related to metastases.We have modified our text as advised (see Page 8, line 175-177, Page 10, line 206-209 and Page 11, line 221-222). Relevant content is marked in red in the revised manuscript.

Changes in the text:

1. It was recommended to use capecitabine, vinorelbine, or eribulin for breast cancer patients with distant metastases following prior treatment with anthracycline and taxane (29).

2. 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 (33).

3. Trastuzumab plays a prominent role in adjuvant therapy, neoadjuvant therapy and metastatic therapy of breast cancer.

Comment 2: Local therapy for BCLM including surgery, intervention, and radiotherapy is not standard due to the lack of randomized data on survival benefit. The authors should mention the critical view about the benefit of local therapy.

Reply 2: Indeed, local therapy is not currently the standard treatment option for BCLM. Although some studies have shown its benefits on survival, it also has the limitations. We have added these in the article. We have modified our text as advised (see Page 3, line 48-51, Page 12, line 246-247, Page 12, line 252-253, Page 13, line 278-281 and Page 15, line 328-331).

Changes in the text:

1.Some research also reported the improvements of local treatments in survival, although further studies are required to determine more specific selection criteria for these treatments of BCLM. It is difficult to define the role of surgery or less-invasive local procedures in the treatment of BCLM.

2. However, contrary to the substantial evidence for treating colorectal liver metastases locally, there is limited data on resection of BCLM.

3. A limited number of BCLM patients are eligible for surgery because of the extent and location of the disease and physical condition, nevertheless.

4. 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 (51).

5. A report showed 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 (64).

Comment 3: It would be better that the authors specifically describe the point which has not been fully uncovered about the mechanism of BCLM and lack of clinical management for BCLM, so that readers and researchers can understand the issues they have to deal with.

Reply 3:

The mechanism of BCLM is complex, and we have presented relatively critical steps associated with metastasis and major deficiencies in clinical management. More details are still in the exploration stage, and we will further probe and supplement them in the future.

Comment 4: Please describe the limitation and quality of this narrative review.

Reply 4: We have modified our text as advised (see Page 16, line 345-348, Page 17, line 353-354 and Page 17, line 356-358).

Changes in the text:

1. We demonstrated the major mechanisms related to metastasis and the currently available treatment options in the management of BCLM in the article. The process of BCLM is multi-step and there may be other factors affecting the metastasis process and potential mechanisms of it waiting to be explored further.

2. However, because of the lack of clinical data, there are still no specific standard-of-care therapeutic strategies indicated for patients with BCLM.

3. How to choose a more efficacious management to improve prognosis of the patients needs to be probed in the future.

Review Comments (Round 2)

Reviewer A

Comment 1: As I pointed out in the first review that you should correlate the clinical trials and metastatic mechanisms if you would like to discuss both basic metastatic mechanisms and clinical outcome in this review. You only mentioned the details of basic research and clinical trial outcomes separately.

Reply 1:

Many thanks to the reviewer for giving us valuable suggestions. It is important to correlate the clinical trials and metastatic mechanisms. Liver metastasis frequently occurs in breast cancer patients; however, it is a bitter truth that the available treatment options are ineffective and limited. The current therapeutic approaches for breast cancer liver metastasis include palliative therapy (radiation) and hormonal- or HER2-targeted therapy with respect to the presence of receptors. Therefore, we inproved the details of the correlation between the mechanism and clinical trial results of VEGFR-related blocking. At the same time, the basic information of HER2-targeted therapy was added in the corresponding position. **We have modified our text as advised (see Pages 10-11, lines 210-225).** Relevant content is marked in green in the revised manuscript.

Changes in the text:

Breast cancer cells in the liver thrive in a microenvironment characterized by the absence of a sub-endothelial basement membrane and fenestrated endothelium in sinusoidal capillaries (40). The binding of VEGFs to the VEGFR1-3 receptors activates the VEGF signaling pathway in endothelial cells (41). Therefore, it indicated that 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 anti-angiogenic 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 having liver metastases and being pregnant, the patient maintained a complete clinical response for approximately five years (42). This finding suggested that blocking VEGF pathways with drugs such as bevacizumab could be considered a good treatment option for metastatic breast cancer.

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 (43). 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).

Comment 2: The format of the paper, i.e., methods, results and discussion, is very important. You should at least follow the form of the paper.

Reply 2:

Many thanks to the reviewer for your advice. We also think the form of the paper is significant. We have presented an introduction, methods, and discussion and amended the text accordingly further. **We have modified our text as advised (see Page 16, line 337).** Relevant content is marked in green in the revised manuscript.

Reviewer B

I think the manuscript has been improved as a result of your revision. However, it still needs revision, especially in drug-therapy section.

Comment 1:

#1 About drug-therapy

#1-1 It would be better to discuss the treatment for BCLM using subgroup analysis of liver metastasis or visceral disease in pivotal studies of each treatment.

Reply 1:

Many thanks to the reviewer for your valuable advice. It is significant to discuss the treatment for BCLM using subgroup analysis indeed. However, there are still no treatment standards for specific subgroups of BCLM currently. As we know, various subgroups of BCLM are closely associated with treatment and prognosis. In the future, it is necessary to further study the subgroups of BCLM, which is helpful for further early diagnosis and treatment of patients. It might be possible to quantitatively and qualitatively analyze mRNA expression in specific tissues or cells by DNA sequencing and immunohistochemistry, etc. to distinguish different subgroups so as to reveal relevant biological mechanisms and provide potential ideas for the individual and specific treatments. For some studies of treatments in this paper, we described further by using subgroup analysis. **We have modified our text as advised (see Page 8, lines 158-164, and Page 11, lines 225-233).** Relevant content is marked in green in the revised manuscript.

Changes in the text:

In this trial, status of homologous recombination (HR) deficient significantly related to higher objective response rate (ORR) and longer PFS in GP group than in GT group (71.9% versus 38.7%, P = 0.008; 10.37 versus 4.30 months, P = 0.011). And Patients with germ-line BRCA1/2 (gBRCA1/2) mutation had numerically higher ORR and longer PFS in GP group than in GT group (83.3% versus 37.5%, P = 0.086; 8.90 versus 3.20 months, P = 0.459). Germ-line mutations of BRCA1/2 and HR panel are potential biomarkers for better performance of cisplatin-based regimens.

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 those patients receiving HER2-targeted therapy. A phase III randomized clinical study indicated that for patients with hormone receptor-positive and HER2-positive MBC subgroup, in contrast to the single targeted drug (lapatinib/trastuzumab) combined with aromatase inhibitor therapy, the PFS was significantly prolonged when these two targeted drugs combined with aromatase inhibitor therapy (44). This combination provides an effective and safe alternative treatment option to chemotherapy for this patient population subgroup.

Comment 2:

#1-2 Why do you mention CBCSG006 and SOLAR-1 trials among many pivotal studies? Are they specifically associated with BCLM?

Reply 2：

Many thanks to the reviewer for a worthy recommendation. It is a bitter truth that there are still few studies about BCLM and the available treatment options are ineffective and limited. We mentioned the CBCSG006 trial to illustrate that cisplatin-containing combination regimens improved better in terms of survival than progression-free survival (PFS) paclitaxel combination regimen, which might be possible to be applied in the treatment of BCLM. In the SOLAR-1 trial, the PI3K inhibitor alpelisib combined with fulvestrant also increased median PFS in specific patients with MBC. We added the parts of this trial that are relevant to BCLM, and some studies involved BCLM. **We have modified our text as advised (see Page 10, lines 198-200, and Pages 8-9, lines 172-179).** Relevant content is marked in green in the revised manuscript.

Changes in the text:

This trial also indicated median OS (95% CI) in patients with BCLM was 37.2 months (28.7-43.6) and 22.8 months (19.0-26.8) in the alpelisib-fulvestrant and placebo-fulvestrant arms, respectively [HR = 0.68 (0.46-1.00)] (37).

Hepatic arterial treatment (HAT) combined with chemotherapy has also gradually attracted increasing attention. A study suggested HAT oxaliplatin in combination with capecitabine for liver metastases in patients with MBC had high response rates of 42.3% (95% confidence interval (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, the chemotherapy treatment had 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).

Comment 3:

#1-3 Your article should include the discussion about the correlation between the basic mechanism of liver metastasis and drug-therapy. For example, what about discussing bevacizumab in drug-therapy section because you mention VEGFR in the mechanism section.

Reply 3：

Many thanks to the reviewer for giving us valuable suggestions. This time, we inproved the details of the correlation between the mechanism and clinical trial results of VEGFR-related blocking. At the same time, the basic information of HER2 targeted therapy was added in the corresponding position. **We have modified our text as advised (see Pages 10-11, lines 210-225).** Relevant content is marked in green in the revised manuscript.

Changes in the text:

Breast cancer cells in the liver thrive in a microenvironment characterized by the absence of a sub-endothelial basement membrane and fenestrated endothelium in sinusoidal capillaries (40). The binding of VEGFs to the VEGFR1-3 receptors activates the VEGF signaling pathway in endothelial cells (41). Therefore, it indicated that 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 anti-angiogenic 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 having liver metastases and being pregnant, the patient maintained a complete clinical response for approximately five years (42). This finding suggested that blocking VEGF pathways with drugs such as bevacizumab could be considered a good treatment option for metastatic breast cancer.

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 (43). 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).

Comment 4:

#2 It would be better to describe the ongoing clinical trials about liver metastasis, so that the researchers can understand the uncovered point in clinical practice.

Reply 4：

We also think it is essential to describe the ongoing clinical trials. There currently need to be more trials on BCLM. We added recently relevant problems, including the latest one published in 2023, to show the uncovered point in clinical practice. **We have modified our text as**

advised (see Pages 11-12, lines 240-245, and Page 8, lines 164-172). Relevant content is marked in green in the revised manuscript.

Changes in the text:

A recent study by Xie et al. (47) indicated that pyrotinib plus trastuzumab and a single chemotherapeutic agent offered a hopeful choice with manageable safety profile for patients with heavily pre-treated HER2-positive MBC with the median PFS of 7.5 months (95% confidence interval [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.

In addition, the 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) respectively (P = 0.457), and there was no significant difference in OS and PFS between the two groups. And they suggested that eribulin group had less neurotoxicity compared with 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 needs further exploration in the future.