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EDITORIAL

# Consideration on immunotherapy of liver metastases of malignant tumors

Chuang Jiang, Zhi-Hong Zhang, Jia-Xin Li

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## Abstract

In this editorial, we comment on the article "Analysis of the impact of immunotherapy efficacy and safety in patients with gastric cancer and liver metastasis" by Liu *et al* that was published in the recent issue of the *World Journal of Gastrointestinal Surgery*. It has prompted us to think and summarize some thoughts on immunotherapy for malignant tumor liver metastasis. Immunotherapy plays a crucial role in the treatment of malignant tumors; however, the presence of liver metastases in advanced tumors may impact its efficacy. Although patients with liver metastases can still benefit from immunotherapy, multiple clinical studies have indicated that, compared to other sites of metastasis, liver metastases may diminish the effectiveness of immunotherapy. The efficacy of immune checkpoint inhibitors in patients with liver metastases often fails to reach the ideal level, primarily due to the liver metastases exploiting the host's peripheral immune tolerance mechanisms to promote systemic CD8(+) T cell exhaustion, resulting in a systemic immune-tolerant environment. This article aims to summarize the reasons for the decreased efficacy of immunotherapy following liver metastasis in various malignant tumors and propose potential clinical strategies for management.

**Key Words:** Liver metastasis; Immunotherapy; Immune tolerance; Cancer; Treatment

**Core Tip:** Immunotherapy is an important treatment method for solid tumors nowadays. However, liver metastasis leads to a decrease in the efficacy of immunotherapy for malignant tumors. The main reason is that liver metastasis can promote the depletion of systemic CD8(+) T cells by utilizing the host's peripheral immune tolerance mechanism, thereby leading to a systemic immune tolerance environment. In the dilemma of limited efficacy of immunotherapy alone, the combination with chemotherapy, radiotherapy, targeted therapy, and other anti-tumor methods can significantly enhance the efficacy of immunotherapy, holding important clinical prospects.

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## INTRODUCTION

### *Liver metastasis*

Metastases often occur in the advanced stage of malignant tumors. Although different tumors often have different tendencies towards the metastatic organs, the liver is the organ most susceptible to metastasis due to its unique anatomical position, cell metabolism, and immune microenvironment[1]. Liver metastasis substantially impacts patient survival. Studies have shown that patients with liver metastasis have a poorer prognosis compared to those with other organ metastases[2]. There are different pathological types of liver metastasis, with the most common pathologic type reported being not otherwise specified (NOS) adenocarcinoma (74.9%). Most NOS adenocarcinomas originate from the digestive tract (68.2%), especially from the colorectum (46.1%)[3]. There are three different histopathological growth patterns (HGPs) of metastatic cancer cells, including: (1) Desmoplastic type; (2) Replacement type; and (3) Pushing type [4]. Different HGP subtypes have different cytokine profiles and varying levels of lymphocyte infiltration[5]. The HGP of liver metastasis in different tumors is also different. For example, the most common manifestation of liver metastasis in uveal melanoma and breast cancer is replacement type[6,7]; in liver metastases of digestive tract tumors such as gastrointestinal and pancreatic malignancies, the occurrence frequency of the three HGP subtypes is approximately equal [8]. Multiple studies have shown that the prognosis of different HGP subtypes of liver metastasis varies, with patients with desmoplastic HGP having the best prognosis[7,9]. However, some studies have found that patients with non-desmoplastic HGP are more likely to benefit from adjuvant chemotherapy[10]. If HGP can be included in the treatment decisions for liver metastasis patients, it may benefit patients and thus improve their prognosis.

### *Liver metastasis and immune tolerance*

Despite distant metastasis indicating the advanced stage of malignant tumors, in recent years, immunotherapy represented by immune checkpoint inhibitors (ICIs) has become a major breakthrough in the field of malignant tumor treatment, changing the treatment decisions for various solid tumors[11]. For the overall population, immunotherapy provides survival benefits for patients with liver metastasis, but it has been observed in various malignant tumors that the benefits of immunotherapy are significantly reduced compared to patients without liver metastasis. For example, Botticelli *et al*[12] found that the metastasis of urothelial carcinoma to lymph nodes was completely relieved by ICIs treatment, while the metastasis to the liver showed resistance to such treatment. Takeyasu *et al*'s[13] study on non-small cell lung cancer (NSCLC) found that liver metastasis was associated with poorer median progression-free survival (PFS) after treatment with pembrolizumab (3.4 mo *vs* 9.4 mo, $P = 0.0018$). Similar findings were reported by Tumeh *et al*[14], who found that pembrolizumab immunotherapy for melanoma also showed poorer immunotherapy outcomes in patients with liver metastases. A multicenter clinical study on stage IV melanoma showed that the liver metastasis group had poorer response to anti PD-1 monoclonal antibody therapy compared to the non-liver metastasis group, with a significantly lower objective response rate (ORR; 4.3% *vs* 20.7%, $P < 0.05$)[15]. In the recent issue of the *World Journal of Gastroenterology Surgery*, Liu *et al*[16] published an interesting paper revealing that in patients with advanced gastric cancer who received immunotherapy, PFS was significantly worse in the liver metastasis group compared to the non-liver metastasis group (5.0 mo *vs* 11.2 mo, $P < 0.05$). The reason for this clinical phenomenon is currently believed to be liver metastasis leading to immune tolerance.

Liver immune tolerance is a recognized concept[17,18], and it is currently believed that the liver is a key frontline immune organ, with its default immune state mainly being anti-inflammatory or immune tolerance. Under appropriate conditions, the liver is capable of mounting rapid and robust immune responses as well. The balance between immunity and tolerance is crucial for liver function[19]. Peripheral T cells are key participants in adaptive immune responses, and multiple mechanisms lead to depletion or inhibition of peripheral T cells in the liver, resulting in immune tolerance. Preclinical studies have found that metastatic liver cancer can induce systemic tumor-specific CD8(+) T cell loss through the Fas-FasL pathway, leading to reduced efficacy of immunotherapy[20]. Comprehensive sequencing of primary tumors (including melanoma, NSCLC, *etc*.) from patients with metastatic cancer showed a decrease in T cell clonality and diversity, and a decrease in T cell effector capacity in patients with liver metastasis[21]. Tumeh *et al*'s[14] study on biopsy specimens of melanoma liver metastasis found that compared to the non-liver metastasis group, the CD8(+) T cell count at the infiltrating edge of the liver metastasis group was significantly reduced (547 *vs* 1441, $P < 0.05$). Analysis of the distri-

bution of primary tumor and liver metastatic tumor cells in patients with liver metastasis of colorectal cancer by He *et al* [22], revealed that there were more immunosuppressive cells in liver metastases, among which the distribution difference of macrophages was the most obvious. This may be related to intrahepatic immunosuppression and poor immunotherapy efficacy. The lymph nodes, skin, and lungs are areas where anti-tumor immunity is easily beneficial, which may be attributed to the presence of a large number of immune cells in these specific organs[23].

## COMBINATION THERAPY OVERCOMES IMMUNE TOLERANCE

Reversing the immunosuppressive state and improving the efficacy of immunotherapy in patients with liver metastasis are the key to treating liver metastasis. At present, the main approach is to combine another treatment method to improve the efficacy of immunotherapy. However, clinical research on the immunotherapy-based combination therapy for liver metastasis of malignant tumors is limited, with more focus on preclinical studies or case reports (Table 1).

### *Immunotherapy combined with chemotherapy*

The effectiveness of immunotherapy combined with chemotherapy has been demonstrated by multiple studies targeting various malignant tumors. A subgroup analysis of 115 NSCLC liver metastasis patients in the KEYNOTE-189 study found that the combination of pembrolizumab and chemotherapy significantly prolonged the median overall survival (OS) and PFS of patients compared to the chemotherapy combined with placebo group[24]. A meta-analysis that included eight randomized controlled clinical studies showed that PD-1/PD-L1 inhibitors + chemotherapy can reduce the risk of tumor progression (hazard ratio [HR] = 0.60, 95% confidence interval [CI]: 0.55-0.65) and mortality (HR = 0.71, 95%CI: 0.58-0.90) [25]. A study by Inoue *et al*[26] on liver metastasis in colorectal cancer found that the infiltration of CD8(+), CD3(+), and CD56(+) cells in the cetuximab + chemotherapy group was higher than that in the chemotherapy group and no chemotherapy group ($P < 0.05$ for all). The efficacy of combination immunotherapy regimen for liver metastasis of many malignant tumors is worth further investigation. Some phase III clinical studies[27,28] have shown that chemotherapy combined with immunotherapy can improve treatment efficacy and prognosis in advanced gastric cancer patients, but clinical studies on immunotherapy for liver metastasis of gastric cancer are extremely limited. Preclinical studies have also yielded some clinically instructive results. Ho *et al*[29] observed that gemcitabine + PD-1 antibody significantly prolonged the median survival time (66 d *vs* 56 d) of mice with liver metastasis of pancreatic cancer compared with gemcitabine alone. They also found that the combination therapy can enhance the anti-cancer effect and Th1 Lymphocytes response of M1 macrophages.

### *Immunotherapy combined with radiotherapy*

Studies have shown that liver targeted radiation therapy can reshape the liver immune microenvironment, reduce T cell consumption, and restore the effectiveness of immunotherapy[20]. Similar studies on NSCLC have shown that local liver radiation therapy can lead to a higher proportion of CD8(+) T cells and CD4(+) T cells in tumor tissue, and the surface of tumor cells will also express higher levels of PD-1/PD-L1. Therefore, radiotherapy combined with immunization may also be an effective treatment for NSCLC patients with liver metastases[30]. In recent years, the effectiveness of stereotactic body radiation therapy (SBRT) has been confirmed for lung cancer liver metastasis. The addition of SBRT in NSCLC liver metastasis patients can promote the anti-angiogenic effect, enhance the immunogenicity of tumors in chemotherapy and immunotherapy, and thus achieve a synergistic effect with systemic therapy[31]. Xu *et al*[32] reported a case of gastric cancer with liver metastasis, which progressed after chemotherapy and targeted therapy, but, after changing the treatment strategy to PD-1 antibody combined with SBRT, partial response was achieved.

### *Immunotherapy combined with targeted therapy*

In a mouse model of colon cancer liver metastasis, it was found that the anti-tumor effect of blocking PD-1 checkpoint alone was not significant, while immunotherapy combined with VEGF inhibitors significantly improved the therapeutic effect. This indicates that VEGF inhibitors may sensitize the antitumor effects of immunotherapy[33]. At present, the combination of angiogenesis inhibitors and anti-PD-1/PD-L1 has become the first-line treatment for patients with metastatic renal cell carcinoma. In the IMpower150 study[34] for metastatic NSCLC, it was found that for patients with liver metastasis, the atezolizumab + bevacizumab + carboplatin + paclitaxel group (ABCP group) had longer OS and PFS compared to the bevacizumab + carboplatin + paclitaxel group (BCP group). Immunotherapy combined with antivascular therapy is of great significance for patients with liver metastasis.

### *Dual immunotherapy*

Considering the immune tolerance of the liver, the combination therapy of dual drug inhibition at immune checkpoints is expected to have a synergistic effect on liver metastasis patients and achieve better therapeutic effects. The CheckMate 277 study[35] evaluated the efficacy in the nivolumab combined with ipilimumab group and chemotherapy group of advanced or metastatic NSCLC patients. The results showed that the dual immunotherapy significantly improved patient efficacy compared to the chemotherapy group (2-year ORR: 40.0% *vs* 32.8%; median OS: 17.1 mo *vs* 13.9 mo, $P = 0.007$). Although there have been no reports of dual immunotherapy for melanoma liver metastases, CheckMate067 study[36] found that the combined treatment of nivolumab and ipilimumab compared with the monotherapy could improve the OS of melanoma patients, which also suggests that the potential value of dual immunotherapy is worth further exploration.

**Table 1 Immunotherapy-based combination therapy for malignant liver metastasis**

| Cancer | Ref. | Type | Combination | Treatment strategy |
|---|---|---|---|---|
| Lung cancer | Ma *et al*[45] | Clinical study | Immunotherapy + targeted therapy | Anti-PD-1 + anlotinib |
| | Jiang *et al*[46] | Preclinical study | Immunotherapy + targeted therapy + radiotherapy | Anti-PD-1 + anlotinib + radiotherapy |
| | Gadgeel *et al*[24] | Clinical study | Immunotherapy + chemotherapy | Pembrolizumab + pemetrexed |
| | Socinski *et al*[34] | Clinical study | Immunotherapy + targeted therapy + chemotherapy | Atezolizumab + bevacizumab + carboplatin + paclitaxel |
| | Hellmann *et al*[35] | Clinical study | Dual immunotherapy | Nivolumab + ipilimumab |
| Colorectal cancer | Ragusa *et al*[33] | Preclinical study | Immunotherapy + targeted therapy | Anti-PD-1 + VEGF inhibitors |
| | Song *et al*[39] | Preclinical study | Immunotherapy + targeted therapy | Anti-PD-L1 + lipopolysaccharide block |
| | Wang *et al*[47] | Clinical study | Immunotherapy + targeted therapy | Toripalimab + regorafenib |
| | Eng *et al*[48] | Clinical study | Immunotherapy + targeted therapy | Atezolizumab + cobimetinib |
| | Hu *et al*[40] | Preclinical study | Immunotherapy + gene therapy | Anti-PD-1 + relaxin gene therapy |
| | Kadota *et al*[49] | Preclinical study | Immunotherapy + targeted therapy | Anti-PD-1 + dasatinib |
| | Inoue *et al*[26] | Clinical study | Immunotherapy + chemotherapy | Cetuximab + chemotherapy |
| Pancreatic cancer | Ho *et al*[29] | Preclinical study | Immunotherapy + chemotherapy | Anti-PD-1 + gemcitabine |
| | Qiu *et al*[50] | Clinical study | Immunotherapy + targeted therapy | Sintilimab + anlotinib + S-1 |
| | Blair *et al*[51] | Preclinical study | Immunotherapy + targeted therapy | Anti-PD-1 + focal adhesion kinase inhibitor (FAKi) + Anti-CXCR4 antibody |
| | Matsumoto *et al*[38] | Preclinical study | Immunotherapy + targeted therapy | Alpha-galactosylceramide (KRN7000) + angiogenesis inhibitor AGM-1470 (TNP470) |
| | Hu *et al*[40] | Preclinical study | Immunotherapy + gene therapy | Anti-PD-1 + relaxin gene therapy |
| | Zhang *et al*[52] | Case report | Immunotherapy + chemotherapy | Penpulimab + modified FOLFIRINOX |
| Breast cancer | Schmid *et al*[53] | Clinical study | Immunotherapy + chemotherapy | Atezolizumab + nab-paclitaxel |
| | Yu *et al*[20] | Preclinical study | Immunotherapy + radiotherapy | Anti-PD-L1 + radiotherapy |
| | Lee *et al*[21] | Preclinical study | Immunotherapy + targeted therapy | Anti-PD-1 + regulatory T cells targeting therapy |
| | Hu *et al*[40] | Preclinical study | Immunotherapy + gene therapy | Anti-PD-1 + relaxin gene therapy |
| | Ozaki *et al*[54] | Clinical study | Immunotherapy + targeted therapy + chemotherapy | Nivolumab + bevacizumab + paclitaxel |
| Melanoma | Tang *et al*[55] | Clinical study | Immunotherapy + targeted therapy + chemotherapy | Anti-PD-1 + axitinib +TACE |
| | Hong *et al*[56] | Case report | Immunotherapy + cryoablation | Anti-PD-1 + cryoablation |
| | Blomen *et al*[57] | Clinical study | Dual imunotherapy + liver-specific therapies | Nivolumab + ipilimumab + liver-specific therapies |
| Gastric cancer | Xu *et al*[32] | Case report | Immunotherapy + radiotherapy | Anti-PD-L1 + radiotherapy |
| | Wang *et al*[58] | Case report | Immunotherapy + targeted therapy | Camrelizumab + lenvatinib |

| | | | | |
|---|---|---|---|---|
| | Peng *et al*[59] | Case report | Immunotherapy + chemotherapy | AK104 (a PD-1/CTLA-4 bispecific antibody) + mXELOX |
| Gastric hepatoid adenocarcinoma | Liu *et al*[60] | Case report | Immunotherapy + targeted therapy + chemotherapy | Pembrolizumab + bevacizumab + epirubicin + albumin binding paclitaxel |
| Nasopharyngeal cancer | Zhang *et al*[61] | Case report | Immunotherapy + chemotherapy | Anti-PD-1 + TP regimen (nab-paclitaxel + cisplatin) |
| Cervical cancer | Nance *et al*[62] | Case report | Immunotherapy + radiotherapy | Pembrolizumab + Yttrium-90 (Y90) |

### *Other combination therapies*

In clinical practice, in order to improve efficacy, there are often not only dual combination therapies, but also multiple combination therapy methods. For example, the Impower150 study used a combination of four treatment methods to significantly improve the survival of patients[37]. A meta-analysis showed that despite the presence of liver metastasis, the efficacy of bevacizumab + chemotherapy + immunotherapy did not significantly decrease, indicating that the use of targeted therapy and chemotherapy can reverse the systemic immune tolerance caused by liver metastasis in lung cancer[25].

There are still many combination therapy methods that are still being explored in clinical research or continuously attempted in preclinical studies. Matsumoto *et al*[38] found that, the combination of an immune stimulator [alpha-galactosylceramide (KRN7000)] and an angiogenesis inhibitor [AGM-1470 (TNP470)] can significantly inhibit the growth of liver metastases from pancreatic cancer, produce synergistic effects, and improve the therapeutic effect; in a mouse model of colon cancer liver metastasis, the use of lipopolysaccharide trapping system can improve the efficacy of PD-L1 monoclonal antibody[39]. Hu *et al*[40] confirmed that up-regulating the expression of the relaxin (*RLN*) gene can further produce synergistic anti-metastasis effect with PD-L1 in the mouse models of liver metastasis of colorectal cancer, pancreatic cancer, and breast cancer. Although these treatment methods have not yet been translated into clinical applications, basic research is more conducive to developing more scientific combination therapy strategies from the mechanism level, which is conducive to further improving the treatment prognosis of liver metastasis patients through clinical translation.

## SIDE EFFECTS OF COMBINATION THERAPY

The side effects of combination therapy in patients are also an important evaluation indicator for the selection of treatment strategy. Although different combination therapy modes can enhance anti-tumor effects, they inevitably bring different side effects. Compared to using ICIs alone, the incidence of toxicity in combination therapy is higher[41]. The incidence of adverse reactions in immunotherapy combined with chemotherapy is higher than that in combination with targeted therapy or radiotherapy. The combination of ICIs and platinum containing chemotherapy is mainly related to the cytotoxicity of chemotherapy drugs; the combination of VEGF and VEGFR inhibitors can cause hypertension and proteinuria; the combination of liver metastasis radiotherapy is mainly manifested as adverse reactions of the digestive tract[42-44]; and in dual immunotherapy, the combined treatment strategy can also cause relatively more adverse reactions compared to monotherapy[35].

## CONCLUSION

Patients with malignant tumor liver metastasis have a poor prognosis. The liver, as an immune tolerant organ, presents a challenge in clinical treatment due to the decreased efficacy of immunotherapy after liver metastasis. It is of great significance to conduct in-depth research on the characteristics of the liver immune microenvironment and identify potential combination therapy targets for the development of new combination therapy strategies for liver metastasis patients. The combination of immunotherapy with chemotherapy, anti-vascular therapy, or radiotherapy, and dual immunotherapy may all improve the anti-tumor effect of monotherapy. However, current clinical research is still relatively limited, and the safety and effectiveness of combination therapy still need to be further evaluated. In the future, more clinical and translational studies should be carried out to optimize immunotherapy strategies through systematic evaluation schemes, so that liver metastasis patients can gain greater benefits from immunotherapy.

## FOOTNOTES

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