



Combined with interventional therapy, immunotherapy can create a new outlook for tumor treatment

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Abstract: Recent progress in immunotherapy provides hope of a complete cure to cancer patients. However, recent studies have reported that only a limited number of cancer patients with a specific immune status, known as “cold tumor”, can benefit from a single immune agent. Although the combination of immune agents with different mechanisms can partially increase the low response rate and improve efficacy, it can also result in more side effects. Therefore, discovering therapies that can improve tumors' response rate to immunotherapy without increasing toxicity for patients is urgently needed. Tumor interventional therapy is promising. It mainly includes transcatheter arterial chemoembolization, ablation, radioactive particle internal irradiation, and photodynamic interventional therapy based on a luminal stent. Interventional therapy can directly kill tumor cells by targeted drug delivery *in situ*, thus reducing drug dosage and systemic toxicity like cytokine release syndrome. More importantly, interventional therapy can regulate the immune system through numerous mechanisms, making it a suitable choice for immunotherapy to combine with. In this review, we provide a brief description of immunotherapies (and their side effects) on tumors of different immune types and preliminarily elaborate on interventional therapy mechanisms to improve immune efficacy. We also discuss the progress and challenges of the combination of interventional therapy and immunotherapy.

Keywords: Immunotherapy; interventional therapy; tumor; immunomodulation

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Method

The Medline and EMBASE databases were searched using (at a minimum) the following keywords: tumor, immunotherapy, interventional therapy, and immunomodulation. All articles studying the immunomodulatory effect of interventional therapy and interventional therapy combined with immunotherapy for tumors were selected by examining their titles or abstracts. After further exploration of the content, articles containing relevant data were then included and summarized. According to the Grading of Recommendations

Assessment, Development, and Evaluation (GRADE) system, all selected articles were graded by their level of evidence and strength of recommendation. The literature searches were updated until October 2020.

Introduction

Cancer immunotherapy, which artificially stimulates the immune system and improves its natural ability to fight the disease, has long been seen as a hope to cure cancer. In recent years, with the prevalence of immunotherapy,

especially immune checkpoint inhibitors (ICIs), immunotherapy has revolutionized cancer treatment. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) are the two most common checkpoint protein molecules in cancer immunotherapy. CTLA-4 (also named CD152) binds CD80 and CD86 with greater affinity and avidity than CD28, thus enabling the transmission of inhibitory signals into T cells. Ipilimumab is the first Food and Drug Administration (FDA)-approved CTLA-4 inhibitor and was initially used for melanoma treatment (1). Latest research has shown that ipilimumab can also work on non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), as well as bladder and prostate cancers (2,3). Unlike the mechanism of CTLA-4 inhibitors, PD-1 inhibitors maintain the tumor cell inhibitory activity of effector T cells by inhibiting the binding of the PD-1 molecule on T cells to PD-L1 on tumor cells. Similar coinhibitory receptors include lymphocyte-activation gene 3 (LAG3), T cell immunoglobulin (Ig) and mucin domain 3 (TIM3), T cell immunoreceptor with Ig, and immunoreceptor tyrosine-based inhibition motif (ITIM) domains (TIGIT), etc. (4-7). Other passive immunotherapies include lymphocyte therapies [such as chimeric antigen receptor redirected T (CAR-T) cells], cytokine therapies [such as IFN- α and interleukin (IL)-2]. The first two FDA-approved CAR-T therapies, tisagenlecleucel and axicabtagene ciloleucel, target the CD19 antigen, which is found in many B-cell types of cancers. Cytokine therapy either directly promotes effector T cell function, for example, through IFN- α , IL-2, and IFN- γ , or promotes effector T cell infiltration locally in the tumor, such as through CXCL9, CXCL10, CXCL11, CCL2, and CCL5 (8,9).

Active immunotherapies, such as tumor vaccines and oncolytic viruses (OVs), direct the immune system to attack tumor cells by targeting tumor antigens. Cancer vaccines trigger or amplify tumor antigens' presentation to either treat existing cancer or prevent the development of cancer. Sipuleucel-T is a therapeutic cancer vaccine approved by the FDA for metastatic hormone-refractory prostate cancer. OVs are genetically engineered viruses that can selectively infect and replicate in tumor cells and ultimately resulting in tumor cell lysis and immunogenic death (10-16). Several viruses, including herpesviruses, poxviruses, picornaviruses, adenoviruses, paramyxoviruses, parvoviruses, reoviruses, Newcastle disease virus, and rhabdoviruses, have now been clinically tested as oncolytic agents (10). T-Vec is the first FDA-approved oncolytic virus to treat melanoma in patients

with inoperable tumors (13). Some approved immune drugs developed for treating cancers of different organs are listed in *Table 1*.

However, insufficient responses to this innovative therapy have also been found in some cases (17,18), which may be due to different cancers' differential immunophenotypes. A previous study has shown that compared to ipilimumab alone, nivolumab plus ipilimumab (anti-PD-1 plus anti-CTLA-4) can lead to a higher 2-year overall survival (63.8% *vs.* 53.6%) for melanoma patients; however, it can also result in higher treatment-related grade 3-4 adverse events (54% *vs.* 20%) (19). To "warm" cold tumors and thereby increase the response rate while reducing or not increasing immunotoxicity, researchers have tried to combine immunotherapy with other interventions (20) (*Table 2*).

Immunotherapies based on tumor biological properties

Although immunotherapy, especially ICIs, has achieved great success in cancer treatment, insufficient responses to this innovative therapy were also found in some cases (17,18), which may be due to the differential immunophenotypes of different cancers. According to a relatively standardized method of classifying tumor immunophenotypes based on the Immunoscore (21-23), tumors are primarily classified into the following four biological types: hot tumors, T cell-excluded tumors, immunosuppressed tumors, and cold tumors. Tumors of different types well match different immunotherapy strategies (21).

Hot tumors are characterized by high-density lymphocyte infiltration at both the tumor center (TC) and the invasive margin (IM) (21-23). However, infiltrating lymphocytes are depleted because of the imbalance of classical 2 pathways (4), which is caused by the overexpression of tumor cells at some checkpoints. Blocking or stimulating costimulatory receptors (4,24) can correct this imbalance and reactivate T cells to restore antitumor immunity. A relatively higher density lymphocyte infiltration characterizes T cell-excluded tumors at the IM but almost no infiltration at the TC. It has been found that this might be attributable to the lack of signals like CXCL9, CXCL10, and CCL5, which recruit T cells into the TC (8,9), or the formation of physical and biochemical barriers at the IM (25-27). Unlike excluded tumors, which prevent T cells from being recruited to the TC (28), immunosuppressed tumors are characterized by very low lymphocyte infiltration at both the TC and IM.

Table 1 Approved immune agents

Immune agents	Brand name	Approved treatment(s)
CTLA-4 blocker		
Ipilimumab	Yervoy	Metastatic melanoma
PD-L1 blocker		
Atezolizumab	Tecentriq	Bladder cancer
Avelumab	Bavencio	Metastatic Merkel cell carcinoma
Durvalumab	Imfinzi	Bladder cancer, non-small cell lung cancer
PD-1 blocker		
Nivolumab	Opdivo	Unresectable or metastatic melanoma, squamous non-small cell lung cancer, renal cell carcinoma, colorectal cancer, hepatocellular carcinoma, classical Hodgkin lymphoma
Pembrolizumab	Keytruda	Unresectable or metastatic melanoma, squamous non-small cell lung cancer (NSCLC), Hodgkin's lymphoma, Merkel-cell carcinoma (MCC), Primary mediastinal B-cell lymphoma (PMBCL), stomach cancer, cervical cancer
Cemiplimab	Libtayo	Cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC
CAR-T cells		
Tisagenlecleucel	Kymriah/Novartis	Relapsed/refractory B-cell precursor acute lymphoblastic leukemia (ALL)
Axicabtagene ciloleucel	Yescarta/Kite Pharma	Relapsed/refractory diffuse large B-cell lymphoma (DLBCL).
Cancer Vaccine		
Oncophage		Kidney cancer
Sipuleucel-T	Provenge	Metastatic hormone-refractory prostate cancer
Bacillus Calmette-Guérin (BCG)		Early-stage bladder cancer
Oncolytic viruses (OVs)		
ECHO-7 enterovirus	Rigvir	Skin melanoma
Oncorine	H101	Head and neck cancer
Talimogene laherparepvec	Lmlygic	Advanced inoperable melanoma

The main factors contributing to the formation of this immunosuppressive tumor microenvironment (TME) include soluble immunosuppressive factors like IL-10 and TGF- β (29,30) and inhibitory immune cells like type 2 macrophages (M2), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs) (31-35). Integrating almost all of the above immunosuppression mechanisms into one, cold tumors are characterized by no lymphocyte infiltration at the TC or IM and are the most difficult tumor type to clear. To achieve clinical efficacy, it may be necessary to use combination therapy, that is, first enhancing the T cell priming effect (via methods such as tumor vaccines, adoptive T cell therapies, or therapies that can convert a tumor into a vaccine) to turn a cold tumor

into a hot one and then combine with antibodies aimed at classic immune checkpoints. However, these combinations would increase immune-related adverse effects (IRAEs) and require rigorous monitoring during the entire process.

Immune-related adverse effects (IRAEs) and limitations

With their mechanism of action dependent on the physiological immobilization of inhibiting immune activation, ICIs usually have a miss target effect, which leads to immune-mediated inflammation of various organs or tissues (36-39). This can sometimes be serious, with up to 60% of grade 3-5 adverse events occurring when anti-

Table 2 Recruiting clinical trials of interventional therapy combined with immunotherapy

Clinical trial No.	Phase	Status	Conditions	Interventions	Endpoint	Locations
NCT03817736	2	Recruiting	HCC	TACE/SBRT/Immune Checkpoint Inhibitor	Number of patients amendable to curative surgical interventions	China
NCT03937830	2	Not yet recruiting	Hepatocellular Cancer/HCC/Metastatic HCC	Durvalumab/Doxorubicin-Eluting Beads/TACE/bevacizumab	Progression free survival (PFS)	United States
NCT03755739	Not Applicable	Recruiting	Hepatocarcinoma	Hepatic artery infusion of an immunotherapy agent (Pembrolizumab)	1. Overall survival (OS) 2. Complete response (CR)	China
NCT03638141	2	Recruiting	Intermediate Stage of HCC/HCC	DEB-TACE/Durvalumab/Tremelimumab (Cohort A dose)/Tremelimumab (Cohort B dose)	Objective response rate (ORR)	United States
NCT03952065	3	Recruiting	Head/Neck Neoplasm	Neck artery infusion (Toripalimab)	Overall survival (OS)	China
NCT03753659	2	Recruiting	HCC	Pembrolizumab/RFA/MWA	Objective response rate (ORR)	German
NCT02821754	2	Recruiting	Biliary Tract Neoplasms/Liver Cancer/HCC/Cholangiocarcinoma/Bile Duct Cancer	Durvalumab/Tremelimumab/TACE/RFA/Cryoablation	Progression free survival	United States
NCT03949153	1/2	Recruiting	Melanoma (Skin)	Nivolumab Injection/Cryotherapy/Ipilimumab Injection	Number of failures linked to the procedure	France
NCT03630640	2	Recruiting	HCC	Nivolumab Injection/Irreversible electroporation	1. Recurrence rates 2. Local recurrence-free survival	France
NCT04062721	1/2	Not yet recruiting	Colorectal Cancer	Chemotherapy/RFA/In situ immunotherapy		
NCT03757858	1/2	Recruiting	Cancer/Abdominal Cancer/Pelvic Cancer/Metastatic Cancer/Peritoneal Metastases/Liver Metastases	Thermotron RF-8/Adoptive cellular Immunotherapy/Anti-PD-1 antibody/Chemotherapy	Progression free survivor	China
NCT03101475	2	Recruiting	Colorectal Cancer/Liver Metastases	Durvalumab (MED14736)/Tremelimumab/SBRT/RFA	Progression free survivor (PFS)	Austria/France/Germany/Netherlands/Sweden/Switzerland
NCT03864211	1/2	Recruiting	HCC Nonresectable	Thermal ablation Toriplimab	Best overall immune response rate	China

Table 2 (continued)

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Clinical trial No.	Phase	Status	Conditions	Interventions	Endpoint	Locations
NCT04049474	1	Not yet recruiting	Advanced Non-small Cell Lung Cancer	Cryo-Immunotherapy/ Device: ERBOKRYO® CA - Cryosurgical Unit with Flexible ERBECRYO Probe, 1.9 mm outer diameter (ERBE, Inc., Tübingen, Germany)	1. Number of participants with adverse events 2. Overall response rate	United States
NCT04123535	Not Applicable	Not yet recruiting	Undifferentiated Pleomorphic Sarcoma	Device: ExAblate 2000/2100 MRgFUS	1. Feasibility 2. Safety	United States
NCT03080974	2	Recruiting	Pancreatic Adenocarcinoma	Nivolumab/Irreversible Electroporation	Incidence of any device-related adverse events	United States
NCT03823131	2	Recruiting	Metastatic Head and Neck Squamous Cell Carcinoma/ Recurrent Head and Neck Squamous Cell Carcinoma/ Unresectable Head and Neck Squamous Cell Carcinoma	Electroporation/ Epacadostat/ Pembrolizumab	Safety and tolerability	United States
NCT04108481	1/2	Not yet recruiting	Colorectal Cancer Metastatic/Colon Cancer/ Metastatic Colorectal Cancer/Rectal Cancer/ Liver Metastasis Colon Cancer/Colorectal Cancer/Colorectal Adenocarcinoma/ Colorectal Neoplasms/Liver Metastases/Colorectal Carcinoma	Durvalumab/Yttrium-90 Radio Embolization		United States
NCT02913417	1/2	Recruiting	Uveal Melanoma/Hepatic Metastases	SIR-Spheres® Yttrium 90/Ipilimumab/ nivolumab	Determine the maximum tolerated dose	United States
NCT03812562	1	Recruiting	HCC	Nivolumab/Yttrium Y 90 Glass Microspheres	Safety and tolerability	United States
NCT03945162	2	Recruiting	NMIBC Refractory to BCG	TLD-1433 Bladder infusion and Photodynamic Therapy	Recurrence rate	Canada
NCT03727061	2	Recruiting	Recurrent Head and Neck Carcinoma/Locally Advanced Head and Neck Carcinoma	Nivolumab/ Porfimer Sodium/ Interstitial Illumination Photodynamic Therapy/ Pembrolizumab/ Cisplatin/Carboplatin/ Cetuximab/Fluorouracil	Complete response (CR) rate	United States

DEB-TACE, drug-eluting bead transcatheter; SBRT, stereotactic body radiation therapy; RFA, radio-frequency ablation; MWA, microwave ablation; MRgFUS, magnetic resonance-guided focused ultrasound; HCC, hepatocellular carcinoma; NMIBC, non-muscle invasive bladder cancer; BCG, bacillus calmette-guerin.

CTLA-4 and anti-PD-1 are used simultaneously (40-42). Cytokine release syndromes (CRS) are common in patients treated with CAR-T cells. These complications are usually not life-threatening and can be controlled by administering steroids (43), adjusting dosage, or terminating the treatment if necessary. However, the regression of IRAEs caused by steroids can lead to steroid-related immunosuppression, which may also impair the antitumor response (39).

Current studies regarding CAR-T cell therapy have mainly focused on hematological cancer (44,45), while studies regarding solid tumors are still in the early stages (46-51). Although cancer vaccines and oncolytic viruses seem harmless, they are mainly experimental and not extensively used in clinical practice as checkpoint inhibitors, and thus, the long-term toxicity remains unclear. CAR-T cells and vaccines are “autologous”, meaning that the production of personalized CAR-T cells and tumor vaccines involves a high design cost and is time consuming. An OV's efficacy is primarily limited by the low effective bioavailability of the delivery route (52,53). At present, OVs are administered either through intratumoral injection, which greatly limits the scope of application or through intravenous injection, which also greatly weakens their efficacy due to the antiviral immune response.

Interventional therapy and the combination with immunotherapy (Table 2, Figures 1,2)

Due to the rapid development of interventional radiology, including transarterial chemoembolization (TACE), ablation, internal irradiation therapy, and photodynamic therapy (PDT), interventional therapy has become an important means of cancer treatment. Tumor interventional therapy has the advantages of small trauma, rapid recovery, targeting, and repeatability. It can be effectively combined with various modern medical methods and high-tech procedures to achieve a synergistic effect (54). More importantly, local cancer interventional therapy can regulate the immune system through different mechanisms, causing a systemic immune response (21,55,56). Although this effect is too weak to prevent local recurrence or distant metastasis (55), it can expand the effectiveness of immunotherapy and might be a powerful combined strategy for immunotherapy. An ongoing phase II, single arm, multicenter study (NCT03469713) is attempting to analyze the objective response rate (ORR) of nivolumab plus stereotactic body radiotherapy (SBRT) in II and III lines of patients with metastatic renal cell carcinoma (mRCC), with the primary

outcome measure being the frailty status as measured by the SHARE-frailty instrument measurement. This would be the first report on the safety profile of nivolumab in combination with SBRT.

Transarterial chemoembolization (TACE)

Due to the physiological basis of double blood supply in normal liver tissue and the fact that more than 95% of the blood supply of hepatocellular carcinoma (HCC) comes from the hepatic artery, TACE has mostly been applied to advanced unresectable HCC (57-59). It is aimed at killing tumor cells without causing severe adverse effects to normal hepatic tissue. TACE has also been employed as an alternative for resectable early stage HCC and in patients with regional recurrence of the tumor following previous resection and bridge therapy to surgery, radiofrequency ablation (RFA), or liver transplantation for downstaging (60-63). TACE has also demonstrated promising results in unresectable cholangiocarcinoma (64). Other treated malignancies include carcinoid tumors, pancreatic islet tumors, and sarcomas metastatic to the liver, whereas TACE's efficacy in patients with colorectal metastases is possibly palliative.

Immunomodulatory effects of TACE

It has been found that TACE can generate a bidirectional effect on tumor treatment by regulating the immune system. Embolization can lead to tumor tissue necrosis, thus reducing the mass and the release of immunosuppressive factors and weakening immune function inhibition (65). Moreover, necrotic tumor tissue can activate the systemic immune response by changing the phenotype of peripheral immune cells (66). Iodized oil-TACE increases infiltration of glypican 3 peptide-specific cytotoxic T lymphocytes. Embolization with polyvinyl alcohol (PVA) particles increases AFP-specific CD4+ T cells and is positively correlated with tumor necrosis and prognosis (67). On the other hand, embolization also reduces the number of peripheral T helper cells, which weakens the antitumor immune response (65). At the same time, embolization can induce a hypoxic microenvironment and upregulate the expression of vascular endothelial growth factor (VEGF), hypoxia inducible factor-1 (HIF-1), and PD-L1 on immune or tumor cells, resulting in an immunosuppressive effect (68).

Application of TACE combined with immunotherapy

The rational combination of TACE's bidirectional effect

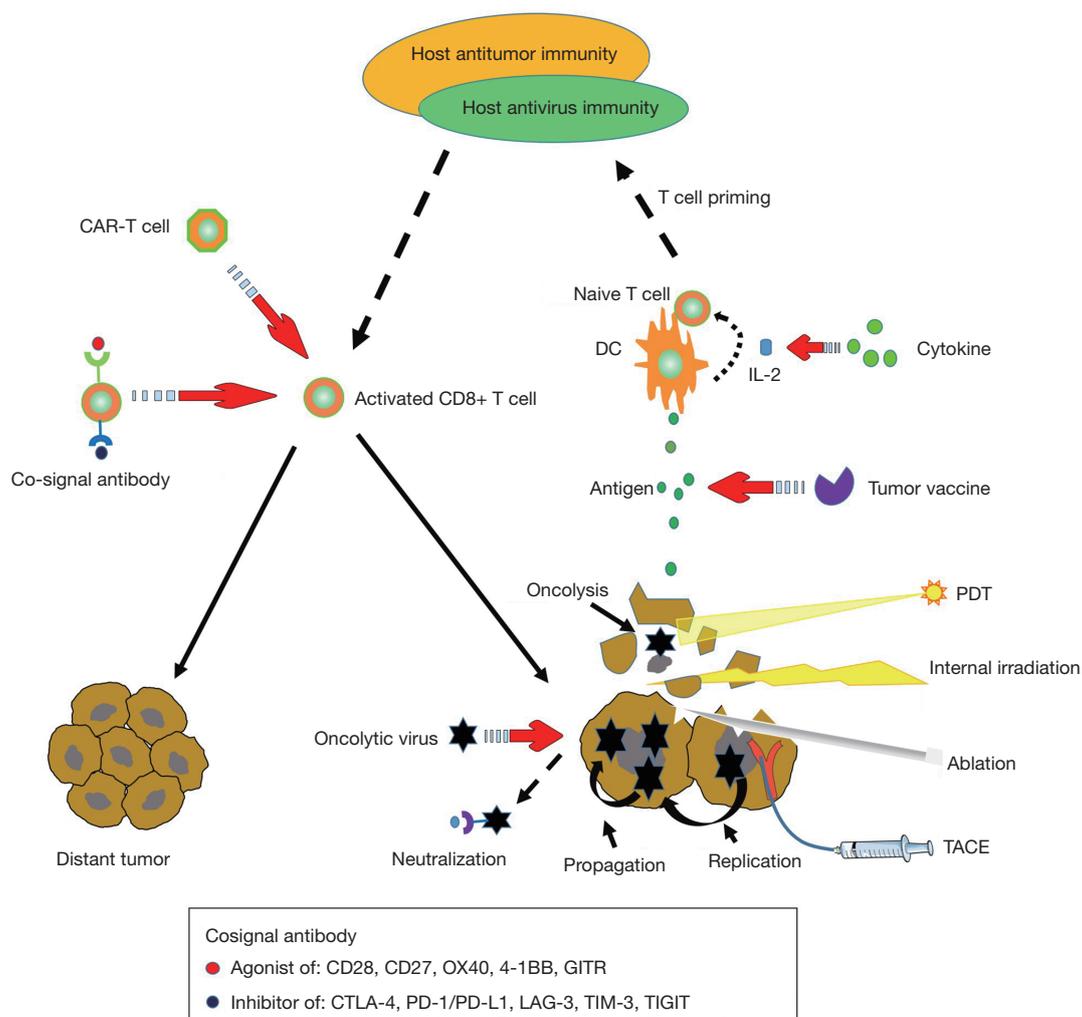


Figure 1 Immune mechanisms triggered by interventional therapies and potential immunotherapy category that could be applied together with interventional modalities. Interventional therapies, such as TACE, ablation, internal irradiation, and PDT, can cause immunogenic stress or death of tumor cells and produce a large number of tumor antigens. These processes can also induce strong inflammatory cell responses that promote DC maturation and increase the secretion of cytokines, such as chemokines, which drive the antigen presentation process. These specific antigens activate the maturation of immature T cells and promote their proliferation. Receptors on the surface of T cells can also bind to coinhibitory signals to inhibit the activation of T cells. As a foreign substance, OVs can also be recognized as foreign antigens. Antigenic "educated" T cells "patrol" throughout the body to seize those specific antigens, leading to the regression of distant tumors (or viruses). Immunotherapies such as OVs, tumor vaccines, CAR-T cells, nonspecific immunotherapy (cytokines such as CCLs, CXCLs), and cosignal antibodies (OX40, 4-1BB, anti-CTLA-4, anti-PD-1 etc.), can enhance the production of effector T cells and assist in killing tumor cells, and have a synergistic effect in combination with interventional therapies. TACE, transarterial chemoembolization; DC, dendritic cell; OVs, oncolytic viruses; CAR-T cells, chimeric antigen receptor redirected T cells.

on the immune system and immunotherapy is expected to achieve synergistic therapeutic effects (69). Duffy *et al.* (70) reported on a heavily pretreated post-sorafenib patient population with HCC who received two doses of tremelimumab followed by TACE. The result showed

encouraging clinical activity, with 2/8 patients achieving a partial response, as well as a median overall survival (OS) of 13.6 months [95% confidence interval (CI): 7.5 months-undefined] and a median potential follow-up (from the study date until analysis) of 18.8 months. He *et al.* evaluated the

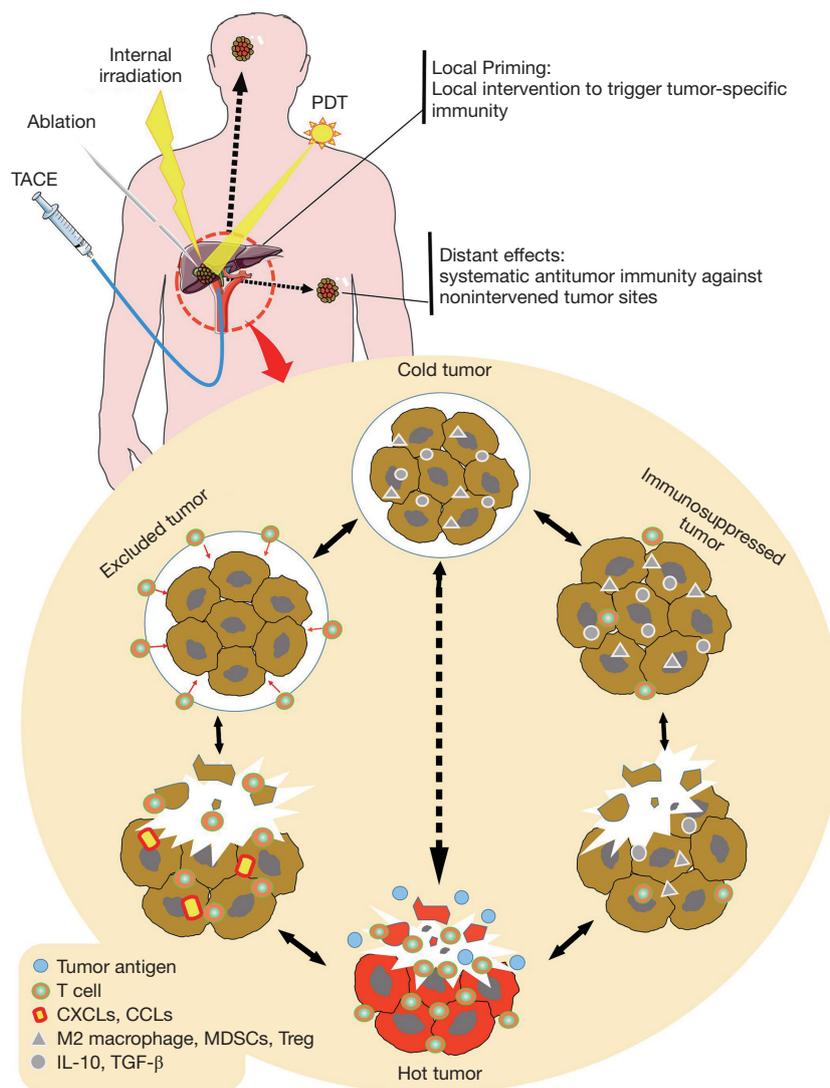


Figure 2 Immunomodulatory activity of interventional therapies on tumors with different immune status. Interventional therapy can transform tumors (such as cold tumors, excluded tumors, and immunosuppressed tumors) with no or low response to immunotherapies into hot tumors through a variety of mechanisms, including promoting immunogenic stress and death, forming an inflammatory environment, exposing antigens and reducing the tumor load, breaking physical and immunosuppressive biochemical barriers, etc. However, interventional therapies may also produce immunosuppressive factors such as IL-6, HIF-1 α , HGF, and its receptor c-MET, which can upregulate the expression of PD-L1 and deepen the immunosuppressive state of tumors. IL-6, interleukin 6; HIF-1 α , hypoxia-inducible factor 1 alpha; HGF, hepatocyte growth factor; PD-L1, programmed death-ligand 1.

efficacy of recombinant human type-5 adenovirus (H101) in patients with unresectable HCC treated by TACE (71). Compared with TACE monotherapy, patients treated with combined TACE and H101 therapy had increased OS rates (61.0%, 40.0%, and 31.5% *vs.* 55.0%, 33.4%, and 22.3%, for estimated 1-, 2-, and 3-year OS, respectively) and decreased cancer-specific mortality. Another case with

recurrent HCC treated with a transarterial injection of H101 combined with TACE also led to a good clinical prognosis with no evidence of recurrence, no abnormal liver function, and a normal serum AFP level 18 months after the last H101/TACE treatment (72). Huang *et al.* tried to determine the clinical efficacy of sequential therapy with RFA and TACE compared to the autologous cytokine-

induced killer (CIK) cell transfusion combined with RFA and TACE in the treatment of HCC. They found that the patients in the TACE + RFA + CIK group had a significantly longer OS (56 *vs.* 31 months, $P=0.001$) and progression-free survival (PFS) (17 *vs.* 10 months, $P=0.001$) than those in the TACE+RFA group. They concluded that CIK cell immunotherapy might effectively prevent recurrence and metastasis in HCC patients after RFA and TACE (73).

Guo *et al.* studied patients with small-cell lung cancer and metastatic liver cancer who failed to achieve disease control after radiotherapy and chemotherapy and subsequently received TACE for liver metastasis and four courses of nivolumab-based immunotherapy. The results showed a sustained regression of hepatic and pulmonary lesions on imaging and a PFS of 15 months. The researchers concluded that TACE combined with nivolumab can enhance the antitumor immune responses and that there is a synergy between these two treatment modalities (74).

TACE's most frequently reported side effect is the self-limited post-embolization syndrome, which involves pain, fever, nausea, fatigue, and elevated transaminases (75). Other uncommon but serious complications include ischemic cholecystitis, pulmonary or cerebral embolization resulting from non-target embolization, and symptomatic hypothyroidism resulting from the contrast's high retained iodine load. Specialized techniques and devices may decrease the risk of adverse effects. In debilitated patients with advanced disease or impaired liver function, treatment-induced liver failure may offset the intervention's antitumoral effect or survival benefit. A prudent standard is required when selecting candidates for considering the possible complications of the procedure against its potential benefits.

In theory, TACE kills tumor cells via the following mechanisms: the embolic particles coated with chemotherapeutic drugs can not only interrupt the tumor blood supply and stall its growth but also locally and slow-release chemotherapy, allowing for the delivery of a higher dose *in situ* while simultaneously reducing systemic exposure (76). Meanwhile, less than half of large treated lesions demonstrate extensive necrosis in pathology (77), which might be a result of the upregulation of VEGF, HIF-1, and PD-L1 (78,79).

Ablation

Local ablative therapy has been applied for symptom palliating in patients with advanced tumors of the lung (80),

kidney, bone (81), pancreas, and bile duct (82), as well as liver cancer with a small mass or at special sites where the tumor is directly abutting surrounding structures (such as the liver capsule, gallbladder, vessel, diaphragm, intestine, and adrenal gland), with a maximum distance of 1.0 cm between the tumor and these organs (83). It has also been utilized in the treatment of some benign lesions like osteoid osteomas (84-86), uterine fibroids, Morton's neuroma (87), skin lesions (88), and varicose veins. Furthermore, ablation has also been performed to treat precancerous lesions or oligo-progressive tumors. Numerous clinical trials have demonstrated that RFA is a safe and effective treatment for Barrett's esophagus, with more than 80% of patients achieving complete eradication after approximately two to three treatments (89-92). In patients with oligometastatic and oligoprogressive NSCLC, which is defined as those with limited metastatic disease, and in selected individuals with resistance to targeted therapies, evidence for the clinical benefit of local ablative therapy is increasing (57,93). This includes RFA, microwave ablation (MWA), laser and high-intensity focused ultrasound (HIFU) ablation, irreversible electroporation (IRE), and cryoablation.

Immunomodulatory effects of ablation

Ablation can lead to local coagulation necrosis of tumors and can also improve the antitumor immune response through the following mechanisms:

- (I) Increasing the exposure of tumor antigen: ablation leads to immunogenic death of the tumor and exposure of a large number of tumor antigens, allowing the tumor to act as an "in situ vaccine" (93,94).
- (II) Enhancing the immunogenicity of tumor antigens: heat shock proteins (HSPs) can act as carriers or peptide chaperones to bind to tumor antigens in order to form HSP complexes, which are presented by major histocompatibility complex (MHC) I molecules to activate CD4+/CD8+ T cells to induce specific cellular immunity against tumor cells. Ablation can increase HSP expression in tumor tissues and the periphery, thereby enhancing the immune response to HCC (95-97).
- (III) Activating antigen-presenting cells (APCs) to increase tumor-specific T cells: dendritic cells (DCs) are the most powerful APCs. When the local infiltration of DCs in tumors is insufficient or dysfunctional, which can lead to reduced cytokine release, the interaction of MHC-peptide complexes

with T cell receptors does not lead to T cell expansion but rather to T cell tolerance (98,99). Ablation can activate local DCs to proliferate and mature, and effector T lymphocytes to exert antitumor effects by presenting tumor antigens and releasing costimulatory signals and cytokines (55,56).

- (IV) Reducing immunosuppression: it has been found that ablation might reduce the release of immunosuppressive factors like CD25⁺Foxp⁺ Tregs (55).

Application of ablation combined with immunotherapy

The immune response that is stimulated by energy-based ablations alone is often too modest to completely expunge established tumors (100). A clinical trial of the CTLA-4 inhibitor tremelimumab combined with ablation in the treatment of advanced HCC (70) showed that, compared with tremelimumab alone, the combined therapy not only effectively controlled the lesions but also increased the accumulation of cytotoxic T cells in distant untreated lesions, increasing the objective response to immunotherapy. Bäcklund *et al.* reported a case of lung metastasis from colorectal cancer that remained uncontrolled after multiple surgical resections and stereotactic radiotherapy. After MWA combined with pembrolizumab, no new lung lesions or tumor recurrence were found during the 8-month follow-up (101). Three RFA cycles followed by the intravenous atezolizumab were performed in a case of recurrent squamous cell lung cancer in the left lower lobe after resection of the left upper lobe, as well as four cycles of adjuvant chemotherapy. The results showed that one lesion in the left lower lung that received RFA combined with atezolizumab displayed remarkable control, while another lesion in the right upper lung treated with the only atezolizumab showed little improvement (102). Another case reported by Soule *et al.* (103) showed that treatment of metastatic renal cell carcinoma (RCC) with percutaneous cryoablation and local administration of nivolumab could enhance the systemic immune response to metastatic bone lesions.

Studies in mouse models of prostate cancer (104) showed that local cryoablation of tumors did not affect distant secondary tumors' growth, whereas the combination with CTLA-4 inhibitors significantly slowed the growth and even eliminated secondary tumors. Compared with the cryoablation monotherapy group, the combination therapy group had more cytotoxic T cell infiltration in distant

secondary tumors and a higher cytotoxic T cells ratio to Tregs. Similar results were also observed in melanoma (93) and colon cancer (105) models in mice. Qian *et al.* found that NOD scid gamma mice inoculated with the human melanoma WM115 cell line and then infused with chondroitin sulfate proteoglycan-4 (CSPG4)-specific CAR-T cells followed by photothermal ablation of the tumor showed more evidence of tumor decay, indicating that photothermal therapy facilitates the accumulation and effector function of CAR-T cells within solid tumors (106). Blanchard *et al.* found that direct cell ablation by stereotactic body radiation therapy (SBRT) not only generated excellent control or cure of local, clinically detectable and accessible tumors but also induced relatively weak T cell responses, which could be boosted by systemically administered VSV-TAA, contributing to the control of local and systemic disease (107). Zhao *et al.* treated a murine orthotopic pancreatic ductal adenocarcinoma model (KRAS* model) with irreversible electroporation and anti-PD1 and found that the combined therapy significantly prolonged the survival of the model and achieved a cure rate of 36–43% with a memory T cell response. The combined therapy also promoted tumor infiltration by CD8⁺ cytotoxic T cells without recruiting other immunosuppressive cells (108).

However, to date, due to the lack of high-level evidence-based medicine and prospective clinical studies with the multicenter, large sample, and randomized control, ablation therapies are only used as an alternative or complementary treatment in solid tumors except for some primary small liver cancers. Also, the therapeutic and side effects vary between different ablation equipment. Ablation can also promote the growth and metastasis of distant tumors by promoting the production of IL-6, HIF-1 α , hepatocyte growth factor (HGF), and its receptor c-MET (109–111). These factors can upregulate the expression of PD-L1 (112,113), thereby inhibiting the antitumor immunity effect of ablation.

Internal irradiation therapy

Radioisotopes are implanted into or adjacent to a tumor by interventional means, such as particle scaffolding or stents, to treat the tumor locally. This technique is now widely used to treat various malignancies; for example, iodine-125 seed implantation in prostate cancer, radioembolization of HCC [Yttrium-90 (Y-90)-labeled microspheres], and iodine-125 particle-loaded radioactive stents for malignant tumors of the biliary tract or esophagus and for airway

obstruction. Different studies have suggested that the effect of radioactive particle implantation is comparable to that of surgery and external radiotherapy and is superior to that of surgery when combined with other modalities (114,115).

Immunomodulatory effects of internal radiation therapy

There are currently no direct studies demonstrating the effects of internal radiation therapy on the immune system. The traditional perception is that radiation exposure suppresses immunity; however, studies on external radiation therapy have shown that in some cases, radiotherapy with moderate radiation exposure can activate the immune system and enhance antitumor effects (21,116-120). Radiotherapy can destroy the irradiated tumor and control distant metastasis beyond the local treatment site, known as the "abscopal effect" of radiation therapy (121-123). The possible mechanisms of the activation of the antitumor immune response by radiation therapy are briefly summarized as follows:

- (I) Increasing the exposure of tumor antigen: radiotherapy causes immunogenic death of tumor cells, which induces the release of tumor-associated antigens (TAAs), thus increasing the probability of tumor cells being recognized by T cells.
- (II) Promoting the activation and maturation of DCs: radiotherapy induces immunogenic stress or death of tumor cells, leading to the release of danger-associated molecular patterns (DAMPs) in the TME. DAMPs can bind relevant receptors (124-129) to promote the recruitment, phagocytosis, and migration of DCs, as well as induce the secretion of relevant cytokines by DCs, ultimately presenting tumor antigens to T cells to activate and stimulate the proliferation of T cells (130). The activated effector T cells can enter the circulation to capture tumor antigens, leading to regression of distant tumors (131,132).
- (III) Promoting an inflammatory microenvironment: radiotherapy increases the expression of proinflammatory cytokines (133-138) [such as IL-1 β , TGF- β , FGF, and TNF, as well as the NACHT, LRR, and PYD domain-containing protein 3 (NALP3) inflammasome] and chemokines (such as CXCL9, CXCL10, CXCL11, and CXCL16), which in turn recruit immune cells into the TME. However, the recruited immune cells can be either antitumor immune cells, such as DCs and

effector T cells (139,140), or tumor-promoting immune cells, such as Tregs, MDSCs, and tumor-associated macrophages (TAMs) (132,141-145). Also, radiotherapy converts tumor-associated macrophages into type 1 macrophages (M1) and increases the expression of the tumor endothelial cell adhesion molecules Icam-1 and Vcam-1, which facilitate the recruitment of T cells to tumors (146). Radiotherapy also upregulates the IFN- γ -mediated expression of PD-L1 on the surface of tumor cells (143).

- (IV) In addition to the direct stimulation of the adaptive immune system, deoxyribonucleic acid (DNA) released from the cell injury mediated by radiotherapy can activate and promote the production of interferon type 1 (IFN-1) through Toll-like receptors, RIG-1-like receptors, and stimulator of interferon gene (STING), improving the antitumor immune response mediated by T cells. However, this process requires the infiltration of CD103⁺ DCs into the tumor so that the efficacy could be limited in tumors barren of T cells while being effective in T cell "excluded" tumors (142,143).

Application of internal irradiation combined with immunotherapy

Conventional and simple radiotherapy upregulates the expression of PD-L1 on the surface of tumor cells mediated by IFN- γ and is considered to be one of the most important factors in tumor resistance to radiotherapy (143,147). Studies (143,148) have shown that after conventional radiotherapy in melanoma, colorectal cancer, and triple-negative breast cancer models in mice, the expression of PD-L1 on tumor cells increased, resulting in resistance to radiotherapy. However, radiotherapy combined with PD-1/PD-L1 inhibitors enhances antitumor-specific T cell immune responses and reduces the number of MDSCs in the TME to improve radiotherapy's therapeutic efficacy. Confino *et al.* found that Da3 mice with breast cancer and lung metastasis treated with a combination of DaRT wires in combination with an MDSC inhibitor (sildenafil), Treg inhibitor (cyclophosphamide at low dose), and the immunostimulant, CpG, 3/20 showed complete rejection with primary tumors and elimination with lung metastases. The other mice treated with different strategies also showed a reduced tumor burden and prolonged survival compared to the controls' corresponding outcomes (149).

Kwon *et al.* conducted a multicenter randomized double-blind phase III clinical trial to assess the clinical

efficacy of radiotherapy combined with ipilimumab after chemoresistance in castration-resistant prostate cancer but concluded no significant difference between the groups in terms of OS in the primary analysis (11.2 vs. 10.0 months; $P=0.05$) (150). In another phase, I clinical trial, 22 patients with metastatic melanoma were treated with a combination of radiotherapy and ipilimumab. The analysis showed that 18% of patients had a partial response, 18% were stable, and 64% continued to progress after refusing combination therapy. Furthermore, it was also found that radiotherapy combined with two ICIs with different mechanisms (a CTLA-4 inhibitor and a PD-1/PD-L1 inhibitor) significantly increased the complete response rate of mice with melanoma (151). A phase 2 multicenter trial to determine if combined treatment with PSA/TRICOM vaccine and ^{153}Sm -EDTMP radiation could delay the progression of prostate cancer better than radiation alone showed no significant difference in the primary endpoint and the median PFS (3.7 vs. 1.7 months) ($P=0.041$, HR =0.51, $P=0.046$); 3/21 patients in the combination arm achieved PSA decline >50%, compared with no patients in the ^{153}Sm -EDTMP alone arm >30% (152).

Radioembolization is a minimally invasive technique that combines embolization and internal radiation therapy, in which microspheres containing the radioisotope Y-90 are implanted into the tumor-feeding arteries, resulting in a high dose of radiation to the tumor and blockage of its blood supply. An open-label fixed-dose phase Ib trial (NCT02416466) of CAR-T hepatic artery infusions followed by selective internal radiation therapy (SIRT) with Y-90 Sir-Spheres[®] for CEA-expressing liver metastases has been completed; however, the results have not yet been published. Delivered via the vascular pathway, embolic microspheres can also cause non-target embolization, which could be avoided by taking appropriate measures before administering irradiation particles during the mapping procedure. Post radioembolization syndrome, which involves symptoms such as fever, fatigue, nausea, vomiting, and anorexia, is self-limited and only requires symptomatic management in some patients. However, this therapy may lead to cumulative radiation adverse effects on the medical staff who have been engaged in this work for an extended period.

Photodynamic therapy (PDT)

PDT was first proposed more than 100 years ago (153) and has since been intermittently used in the study of cancer

treatment (154,155). Photosensitizers (PSs), which act as catalysts, can convert molecular oxygen into a series of highly reactive oxygen species (ROS) under visible light exposure. This can kill tumor cells (156-158) via mechanisms such as direct necrosis or promotion of apoptosis to inhibit tumors (159), or cause changes in the tumor vasculature, such as the closure of blood vessels, thus hindering the supply of oxygen and nutrients to tumors (160,161). PDT is highly effective for actinic keratosis of the skin, which could become cancerous, such as non-hyperkeratotic actinic keratosis on the face and scalp (162,163) and actinic cheilitis on the lip (163). PDT has also shown promising efficacy in the treatment of superficial non-melanoma skin cancers (Bowen's disease) (164,165), small uncomplicated superficial basal cell carcinoma (BCC), nodular BCC (162), and some other benign skin conditions (166).

Immunoregulation of PDT

PDT also has a significant effect on the immune system (167-169): (I) PDT can produce acute inflammation and attract leukocytes to the treated TME; (II) PDT can increase the immunogenicity of dead tumor cells by exposing or producing new antigens and increase the efficiency of antigen cross-presentation by inducing HSPs to form more effective tumor-specific cytotoxic T cells (158); (III) the proinflammatory effect of PDT may also increase DC migration, antigen uptake, and secretion of cytokines; and (IV) PDT can produce long-lasting tumor-specific immune memory.

Application of photodynamic therapy combined with immunotherapy

In a bilateral murine 4T1 breast cancer model, photodynamic therapy was used to intervene on one side of the tumors and was combined with a PD-L1 antibody's systemic administration. The results showed that combined therapy effectively killed the local tumor directly after exposure to light and significantly prevented distant metastasis, and even reduced the size of the existing tumors on the opposite side (170,171). Also, cytotoxic T-lymphocyte (CTL) infiltration was significantly increased in distal tumors unexposed to light in the combination treatment group. The CTL infiltration levels in the control groups were not significantly affected, indicating that photodynamic therapy can reverse the immunosuppressive microenvironment within tumors and trigger CTL-mediated antitumor immunity. Ou *et al.* (172) used photodynamic therapy combined with imatinib to treat melanoma in mice (C57BL/6 mice) and found that

photothermal and photodynamic effects could directly lead to tumor cell apoptosis, necrosis, production of TAAs, and maturation of DCs, which enhanced the presentation of TAAs to T cells. Also, imatinib-loaded GTR-PLGA reduced the suppressive function of Tregs, thereby activating CD8⁺ T cells. Gil *et al.* treated subcutaneously implanted syngeneic murine NXS2 neuroblastoma and human FaDu head and neck squamous cell carcinoma xenografts in nude mice with PDT and oncolytic vaccinia virus (OVV). They found that combination therapy could effectively inhibit the growth of primary and metastatic tumors compared with either monotherapy. Moreover, PDT-induced vascular disruption made the OVV-EGFP infection easier and resulted in higher intratumoral viral titers than those of the untreated tumors (173).

PDT has a good immunomodulatory effect and may induce positive therapeutic effects for malignant obstruction of the digestive tract and ureter or other superficial tumors. However, a meta-review (174) demonstrated a markedly higher average recurrence rate for squamous cell carcinomas treated with PDT (26.4%) than other modalities, including standard surgical excision (5.4%), cryotherapy (0.8%), curettage and electrodesiccation (1.7%), Mohs (3.0%), and radiation (6.4%). Therefore, they concluded that PDT indications should exclude lesions over 2 cm, polymorphic lesions where biopsy may not represent the true histologic sample, and any lesions with dermoscopic characteristics of invasive SCC. Also, other disadvantages, including the time commitment (3-hour incubation period) and pain, are often outweighed when patients have multiple superficial BCCs, Gorlin syndrome, propensity for hypertrophic scarring, as well as a diseased lumen with malignant stenosis.

Future challenges and opportunities

The combination of interventional therapy and immunotherapy has presented new opportunities in the field of tumor research and treatment and has broad application prospects (Table 2). However, numerous relevant studies are still in their infancy, and many key questions need to be addressed.

Firstly, the dose and frequency of combination therapy need to be determined: (I) Dose and frequency of immunologic preparations: the dose and frequency schemes of immune agents currently used in most combination therapies are based on previous experience in clinical trials and need to be evaluated and adjusted during use. Moreover, no consensus has been reached. Considering

the immunomodulatory effects and the local drug delivery function of interventional therapy and the aim of minimizing the immunotoxic side effects, the dose of immune agents is bound to decrease. (II) Amount and frequency of interventional therapy: some interventional therapies, such as ablation and internal irradiation therapy, can promote immunoreactivity and produce immunosuppressive effects. Shi *et al.* reported that inflammation induced by incomplete RFA could accelerate tumor progression and hinder PD-1 immunotherapy (175), suggesting that different effects may be related to the dose (range and length) of intervention. Also, the immunomodulatory effects of interventional therapy, such as the “thermalization” of cold tumors, may be transient (176), and thus, whether “thermalization” should be performed regularly needs to be further confirmed by relevant studies.

Secondly, the optimal timing and sequencing of immunotherapy and interventional therapy need to be determined. As previously mentioned, interventional therapy can lead to the release of tumor antigens through a series of mechanisms. Therefore, in theory, simultaneous intervention or intervention followed by immunotherapy, rather than the other way around, can better incite combination therapy's synergistic effects. Therefore, current studies regarding combination treatment with TACE and immunotherapy are designed to administer immunological agents either during or after TACE. Meanwhile, considering the lower median OS and common deterioration of the liver function of TACE (177,178) compared to systemic therapy, Enrico (179) proposed a novel concept for treating intermediate-state HCC with ICIs; initiating first and delaying the use of TACE to the time-point of radiological progression (should this ever occur) and confining it to the targeting of progressive lesions to reduce the proportion of liver parenchyma exposed to the collateral damage potentially caused by TACE. Relative results might worth expecting. Yu *et al.* (180) compared 76 patients with advanced HCC who received radiotherapy before and/or during the administration of nivolumab with nivolumab monotherapy and found that patients who had received previous/concurrent radiotherapy had a significantly longer PFS ($P=0.008$) and OS ($P=0.007$) than those who did not receive radiotherapy. However, this trend was not observed in patients with a history of RFA or TACE (all $P>0.05$).

Thirdly, the administration route and dosage form need to be determined: there are off-target toxicity concerns, especially with immunotherapy approaches targeting TAA

that can target not only tumor cells but also non-tumor tissues that express target receptors, thus predisposing patients to organ damage (38,181-184). Systemic administration is also prone to cytokine storms and produces toxic side effects such as CRS (185). In particular, the greatest challenge to OV's efficacy is adequate drug delivery because systemically administered OVs are rapidly and massively cleared by the body's antiviral immune defenses, greatly reducing their bioavailability (70,186). There is also increased clearance with intratumoral injection (187,188). However, interventional therapy can employ various new and unique carriers, such as polymeric micelles, nanoparticles, drug-loaded microspheres, covered stents, or other implants, to load and deliver drugs to achieve targeted and controlled release. Researchers have found that the extended-release of innate immunity-including agonists of Toll-like receptor 7/8 (TLR7/8) or STING from a biodegradable hydrogel placed in the tumor resection site cured a much higher percentage of animals than systemic or local administration of the same therapy in solution (189). Another study showed that a single intratumoral administration of the adenovirus (Ad)/hydrogel modality might prolong and potentiate the therapeutic efficacy of Ad, modulate the immune reaction in favor of the virotherapy, and enhance intratumoral localization of the virus, ultimately overcoming the limitations of oncolytic virotherapy revealed in recent clinical trials (190).

Also, it should be noted that the "cold" and "hot" classification of tumors has significant potential for guiding treatment; however, it is not the only factor determining the effect of immunotherapy. In contrast, the Immunoscore system itself has inadequacies (28), such as the strict pathological guidelines and experimental manipulation required for immune scoring and deviation from predetermined standardized operating procedures, leading to incorrect quantification of immune scores. In general, to better predict therapeutic efficacy, more comprehensive analysis methods need to be urgently established. This may involve specific imaging technologies of the TME and efficient early biomarkers, such as PD-L1 overexpression, neoantigens, genetic and epigenetic signatures, and microsatellite instability tumor resident memory T cells, matrix-derived immune biomarkers, and increased glycolysis (191-194).

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/qims-20-173>). The authors have no conflicts of interest to declare.

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