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Efficacy and Mechanism of Combining Radiotherapy and Immunotherapy in Stage IV NSCLC

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Abstract

Lung cancer is the leading cause of cancer-related deaths worldwide. About 85% of lung cancer patients have NSCLC; most are diagnosed with stage IV disease at initial presentation. With the continuous development of oncology, immunotherapy or immune chemotherapy has become the first-line treatment for patients with stage IV NSCLC. However, a proportion of patients still develop resistance to the treatment regimen and experience local progression, and primary lung lesion progression is the main progression pattern of stage IV NSCLC. Preclinical and clinical studies have demonstrated that radiotherapy can induce a systemic anti-tumor immune response and that adding local radiotherapy before cancer progression can prolong survival. Therefore, we considered whether adding local radiotherapy before the progression of a pulmonary lesion in stage IV NSCLC patients receiving immunotherapy or immune chemotherapy would be beneficial. The present review focused on the anti-tumor efficacy of radiotherapy and immunotherapy, emphasizing the time of addition of radiotherapy and the safety of combination therapy for stage IV NSCLC and understanding the underlying mechanism.

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ABSTRACT

Lung cancer is the leading cause of cancer-related deaths worldwide. About 85% of lung cancer patients have NSCLC; most are diagnosed with stage IV disease at initial presentation. With the continuous development of oncology, immunotherapy or immune chemotherapy has become the first-line treatment for patients with stage IV NSCLC. However, a proportion of patients still develop resistance to the treatment regimen and experience local progression, and primary lung lesion progression is the main progression pattern of stage IV NSCLC. Preclinical and clinical studies have demonstrated that radiotherapy can induce a systemic anti-tumor immune response and that adding local radiotherapy before cancer progression can prolong survival. Therefore, we considered whether adding local radiotherapy before the progression of a pulmonary lesion in stage IV NSCLC patients receiving immunotherapy or immune chemotherapy would be beneficial. The present review focused on the anti-tumor efficacy of radiotherapy and immunotherapy, emphasizing the time of addition of radiotherapy and the safety of combination therapy for stage IV NSCLC and understanding the underlying mechanism.

KEYWORDS: Stage IV NSCLC, Combination treatment, Immunotherapy, Radiotherapy

INTRODUCTION

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Lung cancer is currently the most prevalent malignancy and the leading cause of cancer-related deaths worldwide, with an estimated 3.1 million deaths in 2040[1]. In China, the incidence of lung cancer has increased significantly in recent years. NSCLC accounts for 85% of lung cancers; stage IV non-small cell lung cancer (NSCLC) is the most common pathological type with a 5-year survival rate of less than 5%, especially in the initial diagnosis[1-4].

The ongoing research into immunotherapy or immunotherapy combined with chemotherapy is now the first-line treatment for stage IV NSCLC. Several clinical trials, such as the IMpower132 Trial[5]and KEYNOTE-189[6], have demonstrated the benefit of immunotherapy or immune-chemotherapy in patients with stage IV NSCLC, especially in patients with a tumor proportion score for programmed death ligand 1 (PD-L1) of 50% or greater. Although most patients with stage IV NSCLC—treated with first-line immunotherapy or immune chemotherapy—achieved good efficacy, a subset of patients developed disease progression. It is remarkable how many ways the disease can progress. Among them, the pattern of progression of lung cancer is known to be primary tumor enlargement, oligometastasis, and extensive metastasis[7]. Xu et al. studied patients with stage IV NSCLC who received immunotherapy for at least 3 months[8]. Oligoprogression (55.3%) was the dominant pattern of immunotherapy resistance. However, oligoprogression is relatively broad, including progression at less than two focal sites. Further, studies have found that the primary tumor lesion is the most important site of lung cancer progression[9, 10]. Furthermore, Puneeth et al. found that 70% of patients with stage IV NSCLC who received maintenance chemotherapy had progression on the primary lung lesion[11]. For primary lesion progression, these patients can benefit from local treatment[12]. Radiotherapy is the most commonly used local treatment for patients with advanced lung cancer. Previous studies have demonstrated that radiotherapy can not only relieve the clinical symptoms of patients with limited metastatic NSCLC but also prolong the survival time of patients[11, 13]. Likewise, Daniel R. et al. investigated the treatment before disease progression in stage IV NSCLC treated with first-line therapy[14]. The authors found that PFS (Progression-Free-Survival) was higher with adding local therapy versus maintenance therapy (14.2 vs. 4.4 months). Consequently, in the process of immunotherapy or immune-chemotherapy in treating patients with stage IV NSCLC, can we achieve better benefits by adding local radiotherapy before lung progression?

Therefore, we reviewed the mechanisms of immunotherapy combined with radiotherapy and clinical trial evidence to discuss the response to radiotherapy in patients with stage IV NSCLC who had received immunotherapy or immune chemotherapy.

SYNERGISTIC MECHANISM OF RADIOTHERAPY COMBINED WITH IMMUNOTHERAPY

Preclinical studies have demonstrated a synergistic effect and a reciprocal interaction between radiotherapy and immunity. Radiotherapy can play an anti-tumor immune effect by regulating the tumor microenvironment[15]. Similarly, immunotherapy can also reduce the drawbacks of radiotherapy, thereby enhancing the anti-tumor effect.

IMMUNE EFFECTS OF RADIOTHERAPY

Radiotherapy can cause immunogenic cell death (ICD) of tumor cells through reactive oxygen species (ROS)-mediated DNA damage[16]. ICD is followed by the release of tumor-associated antigens (TAAs) and endogenous danger signal-damage-associated molecular patterns (DAMPs), such as high mobility group box 1 (HMGB1), adenosine triphosphate (ATP), and calreticulin (CRT)[17-19]. These substances can bind to the surface receptors of dendritic cells (DCs) or be swallowed by DCs, leading to the activation and maturation of DCs[17, 20]. The activated DCs then migrate to the nearby lymph nodes to present antigen information to T cells, thereby promoting the activation and proliferation of T cells and playing an immune-modulatory role. This process is inseparable from the up-regulation of major histocompatibility complex 1 (MHC-I) molecules and costimulatory molecules, such as CD80[21]. Finally, the activated T cells achieve homing to tumor cells and play an anti-tumor immune role. Moreover, dendritic cells (DCs) can also take up damaged cytoplasmic DNA and induce DCs to secrete interferon-β (IFN-β) that can kill tumor cells through the GMP-AMP synthetase-interferon gene stimulator (cGAS-STING) pathway[22, 23].

II. IMMUNOTHERAPY ENHANCES THE EFFICACY OF RADIOTHERAPY

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Studies have reported that not only radiotherapy has immune effects, but immunotherapy also sensitizes radiotherapy, thus playing a synergistic role. Previous research has suggested that radiotherapy does not produce a durable anti-tumor effect, and it can induce an increase in regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). These cells can inhibit anti-tumor immune effects and reduce radiosensitivity through transforming growth factor-β (TGF-β) and interleukin-10 (IL-10)[24, 25]. Immunotherapy, such as the use of PD-1/PD-L1 inhibitors, activates large numbers of CD8+T cells to induce the expression of tumor necrosis factor-α (TNF-α), which in turn suppresses the effect of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), thereby weakening the resistance to radiotherapy and producing a durable anti-tumor effect[26].

Some preclinical studies have demonstrated that radiotherapy can up-regulate the expression of PD-L1, mainly expressed on the surface of tumor cells and antigen-presenting cells (APCs) via the JAK–STAT–IRF and cGAS-STING pathways[27-29]. PD-L1 can bind to PD-1 on the surface of T cells, B cells, NK cells, and other lymphocytes, thereby inhibiting the anti-tumor effect of CD8+T lymphocytes[16, 30]. Therefore, anti-PD-L1 inhibitors can consume part of PD-L1, thus weakening the anti-tumor inhibition effect. Researchers have applied radiotherapy and immunotherapy to mice and found that the expression levels of PD-L1 on DC, tumor cells, and macrophages after radiotherapy were increased compared with that of the same cell population in control tumor cells[31]. This inhibitory effect can be broken by adding PD-1/PD-L1 inhibitors. Therefore, radiotherapy combined with immunotherapy can play a synergistic and complementary anti-tumor role. One experimental study observed improved survival in mice with combined anti-PD-1 therapy and radiation compared with monotherapy, and only a small percentage (15%–40%) of the animals in the combination group survived more than 180 days after treatment. Immunological data revealed that compared with monotherapy, cytotoxic T cells (CD8+/ IFN-γ +/ TNF-α +) were increased, and regulatory T cells (CD4+/ FOXP3) were decreased in the combined treatment group[21].

III. RELATIONSHIP BETWEEN TAMs AND IMMUNOLOGICAL COMBINED RADIOTHERAPY

Studies have demonstrated that radiotherapy can activate tumor-associated macrophages (TAMs). TAMs include M1 macrophages and M2 macrophages. Notably, their effects on cancer are opposed. There is evidence that M1 macrophages can play an anti-tumor role by up-regulating the expression of TNF-α and interleukin-6 (IL-6)[32]. Nevertheless, M2 macrophages can promote the expression of TGF-β and epidermal growth factor (EGF) to produce an immune suppressive effect, thereby promoting the growth and metastasis of tumor cells[33].

Researchers believe that radiotherapy can increase the aggregation of TAMs, especially M2 macrophages. Radiotherapy activates the STAT pathway through the expression of colony-stimulating factor-1 (CFS-1), activating M2 macrophages. The activated M2 macrophages recruit regulatory T cells (Tregs) that inhibit anti-tumor activity, thereby promoting tumor growth[34, 35]. However, the relationship between radiotherapy and TAMs is still being explored. Some studies have suggested that the radiotherapy dose is related to the type of TAMs. For example, low-dose radiotherapy can promote the activation of M2 macrophages, whereas radiotherapy greater than 1 Gy promotes the polarization of M1 macrophages[36].

By contrast, Cao et al. reported that PD-1/PD-L1 inhibitors can induce the transformation of M2 TAMs into M1 TAMs[37]. There is evidence that PD-1/PD-L1 is associated with the polarization of TAMs[38]. Liu et al. found that PD-L1 was significantly elevated in tumor and stromal compartment macrophages compared to other immune cells[39]. PD-1/PD-L1 is highly expressed in TAMs and can induce polarization toward M2 TAMs by transmitting negative regulatory signals and other mechanisms, which are still being explored. In this case, the addition of PD-1/PD-L1 inhibitor can reverse this effect; thereby, it can reduce the amount of M2 TAMs, increase the amount of M1 TAMs, and induce the up-regulation of TNF-α, interleukin-12 (IL-12), and reactive oxygen species, which play an essential role in T cell activation, thus making up for the deficiency of radiotherapy and playing an anti-tumor role[40-42]. Furthermore, other specific mechanisms of immunotherapy-induced polarization of M1 TAMs must be investigated.

IV. ABSCOPAL EFFECTS OF RADIOTHERAPY

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The abscopal effect, that is, radiotherapy, through its immunomodulatory effect, can play an anti-tumor role at the site of the tumor radiation field and induce adaptive immune response at the site of distant metastasis without radiotherapy[43, 44]. Although the specific mechanism of the abscopal effect is not completely clear, studies have proved that the abscopal effect exists. In the process of radiation therapy, radiation can cause cancer cells to die and increase blood flow, change the tumor microenvironment tumor antigen so that activation of CD8 + T cells throughout the body through the blood circulation, including unexposed sites, is beneficial to the immune system and recognizes tumor cells, leading to reduction or disappearance of distant metastatic sites [45, 46]. In a mouse model of anti-PD-1-resistant 344SQNSCLC adenocarcinoma, radiotherapy was used to treat primary tumors, and a trend was found to increase M1 TAMs in abdominal tumors[47]. In another study on the model of primary anti-PD-1 resistance, the combination of anti-PD-1 and radiotherapy for primary tumors significantly reduced the growth of primary tumors and significantly controlled tumors without radiotherapy and reduced spontaneous lung metastasis (abscopal effect)[48].

CURATIVE EFFECT

Recently, preclinical and clinical trials have demonstrated a prolonged survival benefit of immunotherapy combined with radiotherapy in patients with stage IV NSCLC.

Michel et al. found that adding NHS-IL2 immune cytokine and local radiotherapy to first-line palliative chemotherapy reduced tumor size and delayed tumor growth in a lung cancer animal model[49]. The NHS-IL2 consists of human NHS76 (antibody specific for necrotic DNA) fused to genetically modified human interleukin-2 (IL-2). Furthermore, mice models of lung cancer treated with low-dose radiotherapy (LDRT) and anti-PD-1 inhibitors achieved better tumor control and prolonged survival[50].

The enhanced anti-tumor effects of immunotherapy combined with radiotherapy have been confirmed in preclinical studies and demonstrated in several clinical trials.

A study demonstrated a considerable benefit of local control and survival by adding stereotactic radiotherapy (SBRT) in patients with oligoprogression after required resistance to checkpoint inhibitors (ICIs) in stage IV NSCLC [51]. The trial enrolled advanced NSCLC patients receiving at least two cycles of immunotherapy and had minimal progression. The sites of oligometastases in these patients included the lungs, brain, lymph nodes, adrenal glands, liver, and cervical spine. Overall survival after oligoprogression (OS-PO) was 34 months in patients treated with immunotherapy combined with SBRT versus 22 months in patients without SBRT. Many studies have found that immunotherapy combined with radiotherapy has survival benefits, and the radiotherapy site includes not only the primary tumor, such as the lung, but also metastatic sites, such as the liver and brain. As mentioned previously, the most common site of progression of lung cancer after systemic therapy is the primary lung lesion. Therefore, we must explore whether adding lung radiation before the progression of the primary lesion can provide additional benefits or prevention.

The PEMBRO-RT Phase 2 randomized trial enrolled patients with metastatic NSCLC who progressed after at least one chemotherapy regimen[52]. Enrolled patients were randomly assigned using a 1:1 ratio to receive treatment with pembrolizumab after SBRT to the site of lung lesions or lymph node metastases (experimental arm) or without SBRT (control arm). The ORR (Overall-Response-Rate) at 12 weeks was 18% in the control arm vs. 36% in the experimental arm (P = 0.07). Median PFS was 1.9 months vs. 6.6 months (P = 0.19), and median OS (Overall-Survival) was 7.6 months vs. 15.9 months (P = 0.16). Although the experimental arm did not meet the study's pre-defined criteria, it showed an increase in ORR, median PFS, and OS and no increase in toxicity in the SBRT group. Many clinical trials have demonstrated the feasibility of radiotherapy for pulmonary lesions. Li et al. performed a real-world analysis and also found that the median PFS (9 months vs. 5 months) and median OS (30 months vs. 16 months) were both higher with sintilimab plus radiotherapy for stage III or IV NSCLC than with sintilimab alone[53]. Notably, CRT was performed in patients with positive margins or gross residual tumors after surgery. Patients with isolated or local metastases received SBRT or CRT, indicating that lung radiotherapy combined with immunotherapy can improve survival. Regretfully, the study did not focus on the timing of adding radiotherapy, such as before or after the onset of disease progression. Similarly, Ratnayake et al. found that patients with stage

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IV NSCLC treated with nivolumab and radiotherapy as second-line or subsequent therapy had significantly better PFS compared with patients who did not receive radiotherapy (2.8 months vs. 1.3 months, p = 0.02). The study also found that prior or concurrent thoracic radiotherapy was well tolerated and not associated with an increased incidence of pneumonia[54].

Based on these trials, we verified that radiotherapy to the lung lesion combined with immunotherapy prolonged survival among patients with stage IV NSCLC. As studies have demonstrated that the site is most likely to progress after systematic treatment is the primary site, we wanted to explore the feasibility of adding local radiation to the lung before disease progression to prevent disease progression. Michael et al. found that patients with stable or regressed stage IV cancer after systemic therapy had a longer 2-year OS rate with SBRT for metastatic disease than with progressive disease (55% vs. 15%)[55]. Although our literature search was limited, it cannot be denied that radiotherapy of the primary tumor before disease progression is acceptable.

The most frequently used radiotherapy modality in the literature is SBRT. Nevertheless, conventional radiotherapy is commonly used in our actual clinical practice. Can the addition of conventional radiotherapy bring some benefits? Taugner et al. conducted a real-world study of stage III NSCLC and revealed that concurrent chemoradiotherapy followed by the addition of a PD-L1 inhibitor resulted in higher rates of PFS (60.0% vs. 31.8%) and OS (100.0% vs. 70.5%) at 12 months than chemoradiotherapy alone[56]. This study was applied to conventional fractionated thoracic radiotherapy. Although the patients in this trial were not stage IV patients, it suggests that conventional radiation therapy combined with immunotherapy seems to have unexpected benefits. Similarly, the PORT-C randomized trial demonstrated a higher incidence of 3-year disease-free survival (DFS) with the addition of conventional radiotherapy to postoperative adjuvant chemotherapy than with no radiotherapy in patients with pIIIA-N2 NSCLC (40.5% vs. 32.7%)[57].

Thus, we realized that despite their differences in sensitivity and tumor cell death patterns, SBRT and conventional radiotherapy are both essentially radiotherapy[16, 58, 59]. Both SBRT and conventional radiotherapy can induce cell morphology enlargement and cytoskeletal recombination, causing cancer cells to recognize these stimuli and alter gene expression and cell signals and thereby altering the biological process and cell function of cancer cells; cell morphology and cytoskeletal enlargement are found to be dose-independent[60]. Radiotherapy can target the designated dose to the tumor lesion, whereas normal structures outside the tumor receive less dose, minimizing toxic effects on adjacent normal tissues[61]. Radiotherapy can also benefit cancer patients by relieving pain, possibly curing, preserving organ integrity, and cost effectiveness[62]. Radiotherapy, including SBRT and conventional radiotherapy, contributes to local tumor control and enhances anti-tumor immune effects[63]. The antitumor effects of these two kinds of radiotherapy have also been verified in the following clinical practice..

The MDACC trial found that pembrolizumab combined with radiotherapy had a longer median PFS compared with pembrolizumab alone (9.1 vs. 5.1 months, p = 0.52) for stage IV NSCLC[64]. In this study, the ORR (10% vs. 38%, p = 0.11) and median PFS (6.8 vs. 20.8 months, p = 0.03) were increased in the SBRT group compared with the conventional radiotherapy group, but the increases were not significant. Therefore, we believe that conventional radiotherapy for lung lesions in combination with immunotherapy can benefit stage IV patients. The same holds for lung lesions before their development. However, most studies involved in this aspect are SBRT, and a few studies have related to conventional radiotherapy (added before primary lesions progression combined with immunotherapy), which requires further research and exploration.

SAFETY OF COMBINATION THERAPY:

As conventional radiotherapy combined with immunotherapy can benefit patients with stage IV NSCLC, can the adverse effects (AEs) of combination therapy be tolerated?

Adverse effects can occur with any anti-tumor therapy, so toxicity should be considered in the choice of treatment[43]. The ETOPNICOLAS trial studied the safety of nivolumab when added to chemoradiotherapy in patients with stage III NSCLC[65]. Adding nivolumab to conventional radiotherapy was safe and tolerable, with a 23.5% incidence of [?] grade 3 pneumonia. Combination therapy is tolerated in patients with stage III

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NSCLC and those with stage IV disease. A secondary analysis of KEYNOTE-001 found that after a median follow-up of 32.5 months, there was an acceptable safety profile about previous radiotherapy combined with Pembrolizumab for stage IV patients[66]. Although treatment-related pulmonary toxicity occurred in 13% of patients who received chest radiation, compared with 1% of patients who did not, there was no statistical difference in grade 3 or higher toxicity between the two studies. Similarly, William et al. also found that adding thoracic radiotherapy to treating stage IV lung cancer with ICIs can increase toxic effects, especially pulmonary toxicity. However, it is not conspicuous and can be tolerated by patients (3.3% vs. 4.1%)[67]. Notably, a small percentage of patients who received a median dose of 40cGy of chest radiation during or after immunotherapy did not develop symptomatic pneumonitis, compared with a median dose of 60 cGy for most patients. Tian et al. found that it is safe to receive concurrent treatment of lung lesions SBRT and ICIs, defined as ICIs received within 30 days after pulmonary SBRT[68]. In this study, although 10.7% of SBRT+ICIs patients developed grade 3 or higher pneumonia, compared with 0% of SBRT patients ($p<0.01$), the patients tolerated it. In addition, it was found that radiotherapy for two lobes had a higher risk of pneumonia than that for a single lobe (66.75% vs. 7.55%, P=0.028). Here, there seems to be a relationship between the size of the radiotherapy site and toxicity. A toxicity analysis of thoracic radiotherapy combining with immunotherapy found that 3.8% of patients receiving the combination developed grade 3 pneumonia[69]. Among them, the incidence of grade [?]3 pneumonia was slightly higher in patients treated with concurrent ICIs and chest radiotherapy compared with sequential therapy (7.1% vs. 3.9%), but the difference was not significant (P = 0.014). Unfortunately, the distinction between concurrent and sequential treatment is not described here.

When exploring the toxicity of lung radiotherapy combined with immunotherapy, we found that the dose of radiotherapy, the area of the irradiated lung, and the time interval between the two treatments were all related to the toxicity. However, we believed that adding radiotherapy before progression could benefit the aforementioned parameters, but we were unsure about the specific time. Therefore, this present article next focuses on the relationship between the interval time between radiotherapy, immunization, and toxicity.

The PACIFIC study found a slight increase in pulmonary toxicity (33.9% vs. 24.8%) with durvalumab administered between 1 and 42 days after the completion of thoracic radiotherapy[70]. However, the study did not compare conditions at other time points. Another systematic analysis of real-world studies found rates of all grade pneumonia of 35% and grade [?]3 pneumonia of 6%[2]. By contrast, the interval between radiotherapy and immunotherapy was at least 42 days in more than half of the patients. The two studies used the same treatment regimen, but the latter was a real-world systematic analysis. The incidence of pulmonary toxicity was similar. Radiotherapy was added before lung disease progression occurred in the two studies. Andrew et al. conducted a multicenter study and found that local radiotherapy combined with immunotherapy was acceptable[71]. There were 66 patients (50%) who had received radiotherapy before the start of immunotherapy, with a time interval of 71 days between the two treatments, and 56 patients (42%) who started radiation within 14 days of immunotherapy. Patients who received radiotherapy after immunotherapy had an increase in grade 3-5 ir-AEs compared to another arm (8% vs. 4%), but the timing of the addition of radiotherapy was not distinctly associated with grade 3 or higher toxicity (P = 0.45). Other studies have also found that combining radiotherapy and immunization has a high safety profile and tolerable toxicity. Similarly, Donata et al. found that only 6% and 8% of patients receiving immunotherapy combined with chest radiotherapy developed grade 2 pneumonia and grade 2 esophagitis, respectively[72]. In combination therapy, there are inevitably overlapping toxicities, especially pneumonia. However, concurrent (immunotherapy and radiotherapy were started within 1 month) and sequential therapy (within $>$ 1 month and [?]6 months) were not significantly associated with lung toxicity in subgroup analyses.

With the aforementioned studies, the toxicity of concurrent immunotherapy and radiotherapy is similar to that of sequential therapy, and there is no significant difference. What's more, we found that the toxicity of radiotherapy combined with immunotherapy before lung disease progression was tolerable. Nevertheless, we did not rule out that the more the time of radiotherapy and immunotherapy coincide, the more detrimental to patients. It makes sense for more studies to target intervals exceeding 1 month. However, studies in this area are not abundant, and we must further explore the specific time of adding radiotherapy for patients

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with stage IV NSCLC.

CONCLUSION:

Most preclinical studies have demonstrated that radiotherapy can enhance the anti-tumor immune response, and immunotherapy can also synergistically promote the anti-tumor effect of radiotherapy. More clinical studies have also demonstrated that radiotherapy combined with immunotherapy, compared with other treatments alone, has a higher survival benefit, and patients can tolerate its toxic effects. It is also feasible to add local radiotherapy before lung disease progression. It is believed that the same is true for conventional radiotherapy. Although the published literature has limited data, conventional radiotherapy combined with immunotherapy has great promise in treating stage IV NSCLC before the progression of primary focus. However, there are some limitations in the research, such as the few studies on conventional radiotherapy combined with immunotherapy, the specific time to add conventional radiotherapy, a dose of radiotherapy, and anti-tumor predictors are also major challenges. With the continuous development of medicine, more preclinical and clinical studies are urgently needed to explore these issues and challenges before this protocol can be widely used.

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Ethical statement:

Not applicable.

Conflict of intrerest:

The authors declare that they have no competing interests.

Data availability statement:

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

REFERENCES:

[1] LIEVERSE R I Y, VAN LIMBERGEN E J, OBERIJE C J G, et al. Stereotactic ablative body radiotherapy (SABR) combined with immunotherapy (L19-IL2) versus standard of care in stage IV NSCLC patients, ImmunoSABR: a multicentre, randomised controlled open-label phase II trial [J]. BMC Cancer, 2020, 20(1): 557.

[2] WANG Y, ZHANG T, HUANG Y, et al. Real-World Safety and Efficacy of Consolidation Durvalumab After Chemoradiation Therapy for Stage III Non-small Cell Lung Cancer: A Systematic Review and Meta-analysis [J]. Int J Radiat Oncol Biol Phys, 2022, 112(5): 1154-64.

[3] WU M, LIU J, WU S, et al. Systemic Immune Activation and Responses of Irradiation to Different Metastatic Sites Combined With Immunotherapy in Advanced Non-Small Cell Lung Cancer [J]. Front Immunol, 2021, 12(803247.

[4] CHEN J, WEI S, ZHAO T, et al. Clinical Significance of Serum Biomarkers in Stage IV Non-Small-Cell Lung Cancer Treated with PD-1 Inhibitors: LIPI Score, NLR, dNLR, LMR, and PAB [J]. Dis Markers, 2022, 2022(7137357.

[5] NISHIO M, BARLESI F, WEST H, et al. Atezolizumab Plus Chemotherapy for First-Line Treatment of Nonsquamous NSCLC: Results From the Randomized Phase 3 IMpower132 Trial [J]. J Thorac Oncol, 2021, 16(4): 653-64.

[6] GANDHI L, RODRIGUEZ-ABREU D, GADGEEL S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer [J]. N Engl J Med, 2018, 378(22): 2078-92.

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[7] GOMEZ D R, BLUMENSCHEIN G R, LEE J J, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study [J]. The Lancet Oncology, 2016, 17(12): 1672-82.

[8] XU Y, LI H, FAN Y. Progression Patterns, Treatment, and Prognosis Beyond Resistance of Responders to Immunotherapy in Advanced Non-Small Cell Lung Cancer [J]. Front Oncol, 2021, 11(642883.

[9] AL-HALABI H, SAYEGH K, DIGAMURTHY S R, et al. Pattern of Failure Analysis in Metastatic EGFR-Mutant Lung Cancer Treated with Tyrosine Kinase Inhibitors to Identify Candidates for Consolidation Stereotactic Body Radiation Therapy [J]. J Thorac Oncol, 2015, 10(11): 1601-7.

[10] YOSHIDA T, YOH K, NIHO S, et al. RECIST progression patterns during EGFR tyrosine kinase inhibitor treatment of advanced non-small cell lung cancer patients harboring an EGFR mutation [J]. Lung Cancer, 2015, 90(3): 477-83.

[11] IYENGAR P, WARDAK Z, GERBER D E, et al. Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial [J]. JAMA Oncol, 2018, 4(1): e173501.

[12] TANG Y, XIA B, XIE R, et al. Timing in combination with radiotherapy and patterns of disease progression in non-small cell lung cancer treated with EGFR-TKI [J]. Lung Cancer, 2020, 140(65-70.

[13] TUMATI V, IYENGAR P. The current state of oligometastatic and oligoprogressive non-small cell lung cancer [J]. J Thorac Dis, 2018, 10(Suppl 21): S2537-S44.

[14] GOMEZ D R, TANG C, ZHANG J, et al. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study [J]. J Clin Oncol, 2019, 37(18): 1558-65.

[15] SHANG S, LIU J, VERMA V, et al. Combined treatment of non-small cell lung cancer using radiotherapy and immunotherapy: challenges and updates [J]. Cancer Commun (Lond), 2021, 41(11): 1086-99.

[16] CHEN Y, GAO M, HUANG Z, et al. SBRT combined with PD-1/PD-L1 inhibitors in NSCLC treatment: a focus on the mechanisms, advances, and future challenges [J]. Journal of Hematology & Oncology, 2020, 13(1):

[17] TURGEON. G-A, SIVA. A W A A A B S S. Radiotherapy and immunotherapy: a synergistic effect

in cancer care [J]. Med J Aust, 2018,

[18] SEAN P PITRODA S J C, RALPH R WEICHSELBAUM. Integration of radiotherapy and immunotherapy for

treatment of oligometastases [J]. Lancet Oncol 2019,

[19] MONDINI M, LEVY A, MEZIANI L, et al. Radiotherapy-immunotherapy combinations - perspectives and challenges [J]. Mol Oncol, 2020, 14(7): 1529-37.

[20] YU W D, SUN G, LI J, et al. Mechanisms and therapeutic potentials of cancer immunotherapy in combination with radiotherapy and/or chemotherapy [J]. Cancer Lett, 2019, 452(66-70.

[21] ZENG J, SEE A P, PHALLEN J, et al. Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas [J]. Int J Radiat Oncol Biol Phys, 2013, 86(2): 343-9.

[22] RODRIGUEZ-RUIZ M E, VANPOUILLE-BOX C, MELERO I, et al. Immunological Mechanisms Responsible for Radiation-Induced Abscopal Effect [J]. Trends Immunol, 2018, 39(8): 644-55.

[23] MENG L, XU J, YE Y, et al. The Combination of Radiotherapy With Immunotherapy and Potential Predictive Biomarkers for Treatment of Non-Small Cell Lung Cancer Patients [J]. Front Immunol, 2021, 12(723609.

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[24] LIU Y, DONG Y, KONG L, et al. Abscopal effect of radiotherapy combined with immune checkpoint inhibitors [J]. J Hematol Oncol, 2018, 11(1): 104.

[25] FORMENTI S C, DEMARIA S. Combining radiotherapy and cancer immunotherapy: a paradigm shift [J]. J Natl Cancer Inst, 2013, 105(4): 256-65.

[26] BERNSTEIN M B, KRISHNAN S, HODGE J W, et al. Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach? [J]. Nat Rev Clin Oncol, 2016, 13(8): 516-24.

[27] KORDBACHEH T, HONEYCHURCH J, BLACKHALL F, et al. Radiotherapy and anti-PD-1/PD-L1 combinations in lung cancer: building better translational research platforms [J]. Ann Oncol, 2018, 29(2): 301-10.

[28] SATO H, OKONOGI N, NAKANO T. Rationale of combination of anti-PD-1/PD-L1 antibody therapy and radiotherapy for cancer treatment [J]. Int J Clin Oncol, 2020, 25(5): 801-9.

[29] CHEN C, LIU Y, CUI B. Effect of radiotherapy on T cell and PD-1 / PD-L1 blocking therapy in tumor microenvironment [J]. Hum Vaccin Immunother, 2021, 17(6): 1555-67.

[30] PESCE S, GREPPI M, GROSSI F, et al. PD/1-PD-Ls Checkpoint: Insight on the Potential Role of NK Cells [J]. Front Immunol, 2019, 10(1242.

[31] DENG L, LIANG H, BURNETTE B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice [J]. J Clin Invest, 2014, 124(2): 687-95.

[32] QIAO Y, FU E. Advances in the Study of Tumor-associated Macrophages in Lung Cancer [J]. Zhongguo Fei Ai Za Zhi, 2022, 25(1): 34-9.

[33] XU F, WEI Y, TANG Z, et al. Tumorassociated macrophages in lung cancer: Friend or foe? (Review) [J]. Mol Med Rep, 2020, 22(5): 4107-15.

[34] DENARDO D G, RUFFELL B. Macrophages as regulators of tumour immunity and immunotherapy [J]. Nat Rev Immunol, 2019, 19(6): 369-82.

[35] DONLON N E, POWER R, HAYES C, et al. Radiotherapy, immunotherapy, and the tumour microenvironment: Turning an immunosuppressive milieu into a therapeutic opportunity [J]. Cancer Lett, 2021, 502(84-96.

[36] WALTON E L. Radiotherapy and the tumor microenvironment: The "macro" picture [J]. Biomed J, 2017, 40(4): 185-8.

[37] CAO L, CHE X, QIU X, et al. M2 macrophage infiltration into tumor islets leads to poor prognosis in non-small-cell lung cancer [J]. Cancer Manag Res, 2019, 11(6125-38.

[38] LI W, WU F, ZHAO S, et al. Correlation between PD-1/PD-L1 expression and polarization in tumor-associated macrophages: A key player in tumor immunotherapy [J]. Cytokine Growth Factor Rev, 2022, 67(49-57.

[39] LIU Y, ZUGAZAGOITIA J, AHMED F S, et al. Immune Cell PD-L1 Colocalizes with Macrophages and Is Associated with Outcome in PD-1 Pathway Blockade Therapy [J]. Clin Cancer Res, 2020, 26(4): 970-7.

[40] MILLS C D, LENZ L L, HARRIS R A. A Breakthrough: Macrophage-Directed Cancer Immunotherapy [J]. Cancer Res, 2016, 76(3): 513-6.

[41] GAO J, LIANG Y, WANG L. Shaping Polarization Of Tumor-Associated Macrophages In Cancer Immunotherapy [J]. Frontiers in Immunology, 2022, 13(

[42] AMININ D, WANG Y M. Macrophages as a "weapon" in anticancer cellular immunotherapy [J]. Kaohsiung J Med Sci, 2021, 37(9): 749-58.

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[43] LI M, GAN L, SONG A, et al. Rethinking pulmonary toxicity in advanced non-small cell lung cancer in the era of combining anti-PD-1/PD-L1 therapy with thoracic radiotherapy [J]. Biochim Biophys Acta Rev Cancer, 2019, 1871(2): 323-30.

[44] ARINA A, GUTIONTOV S I, WEICHSELBAUM R R. Radiotherapy and Immunotherapy for Cancer: From "Systemic" to "Multisite" [J]. Clin Cancer Res, 2020, 26(12): 2777-82.

[45] WEN L, TONG F, ZHANG R, et al. The Research Progress of PD-1/PD-L1 Inhibitors Enhancing Radiotherapy Efficacy [J]. Front Oncol, 2021, 11(799957.

[46] DOYEN J, BESSE B, TEXIER M, et al. PD-1 iNhibitor and chemotherapy with concurrent IRradiation at VAried tumor sites in advanced Non-small cell lung cAncer: the Prospective Randomized Phase 3 NIRVANA-Lung Trial [J]. Clinical Lung Cancer, 2022, 23(3): e252-e6.

[47] CHEN D, BARSOUMIAN H B, YANG L, et al. SHP-2 and PD-L1 Inhibition Combined with Radiotherapy Enhances Systemic Antitumor Effects in an Anti-PD-1-Resistant Model of Non-Small Cell Lung Cancer [J]. Cancer Immunol Res, 2020, 8(7): 883-94.

[48] WANG X, SCHOENHALS J E, LI A, et al. Suppression of Type I IFN Signaling in Tumors Mediates Resistance to Anti-PD-1 Treatment That Can Be Overcome by Radiotherapy [J]. Cancer Res, 2017, 77(4): 839-50.

[49] VAN DEN HEUVEL M M, VERHEIJ M, BOSHUIZEN R, et al. NHS-IL2 combined with radiotherapy: preclinical rationale and phase Ib trial results in metastatic non-small cell lung cancer following first-line chemotherapy [J]. J Transl Med, 2015, 13(32.

[50] YIN L, XUE J, LI R, et al. Effect of Low-Dose Radiation Therapy on Abscopal Responses to Hypofractionated Radiation Therapy and Anti-PD1 in Mice and Patients With Non-Small Cell Lung Cancer [J]. Int J Radiat Oncol Biol Phys, 2020, 108(1): 212-24.

[51] WANG Z, WEI L, LI J, et al. Combing stereotactic body radiotherapy with checkpoint inhibitors after oligoprogression in advanced non-small cell lung cancer [J]. Transl Lung Cancer Res, 2021, 10(12): 4368-79.

[52] THEELEN W, PEULEN H M U, LALEZARI F, et al. Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer: Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial [J]. JAMA Oncol, 2019, 5(9): 1276-82.

[53] LI S, CHEN K, YANG M, et al. Radiotherapy improves the outcomes of immunotherapy with Sintilimab in non-small-cell lung cancer: A real-world analysis [J]. Front Immunol, 2022, 13(991431.

[54] RATNAYAKE G, SHANKER M, ROBERTS K, et al. Prior or concurrent radiotherapy and nivolumab immunotherapy in non-small cell lung cancer [J]. Asia Pac J Clin Oncol, 2020, 16(1): 56-62.

[55] MILANO M T, KATZ A W, ZHANG H, et al. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study [J]. Int J Radiat Oncol Biol Phys, 2012, 83(3): 878-86.

[56] TAUGNER J, KASMANN L, EZE C, et al. Durvalumab after Chemoradiotherapy for PD-L1 Expressing Inoperable Stage III NSCLC Leads to Significant Improvement of Local-Regional Control and Overall Survival in the Real-World Setting [J]. Cancers (Basel), 2021, 13(7):

[57] HUI Z, MEN Y, HU C, et al. Effect of Postoperative Radiotherapy for Patients With pIIIA-N2 Non-Small Cell Lung Cancer After Complete Resection and Adjuvant Chemotherapy: The Phase 3 PORT-C Randomized Clinical Trial [J]. JAMA Oncol, 2021, 7(8): 1178-85.

[58] RUSTHOVEN K E, KAVANAGH B D, BURRI S H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases [J]. J Clin Oncol, 2009, 27(10): 1579-84.

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[59] ZHANG H, WAN C, HUANG J, et al. In Vitro Radiobiological Advantages of Hypofractionation Compared with Conventional Fractionation: Early-Passage NSCLC Cells are Less Aggressive after Hypofractionation [J]. Radiat Res, 2018, 190(6): 584-95.

[60] WANG X, LU Y, QIN Z, et al. Stereotactic Body Radiotherapy and Conventional Radiotherapy Induce Cytoskeleton Extension and Enlargement of Cell Morphology in Non-Small Cell Lung Cancer [J]. Dose Response, 2021, 19(4): 15593258211064499.

[61] SCHAUE D, MCBRIDE W H. Opportunities and challenges of radiotherapy for treating cancer [J]. Nat Rev Clin Oncol, 2015, 12(9): 527-40.

[62] THARIAT J, HANNOUN-LEVI J M, SUN MYINT A, et al. Past, present, and future of radiotherapy for the benefit of patients [J]. Nat Rev Clin Oncol, 2013, 10(1): 52-60.

[63] DALY M E, MONJAZEB A M, KELLY K. Clinical Trials Integrating Immunotherapy and Radiation for Non-Small-Cell Lung Cancer [J]. J Thorac Oncol, 2015, 10(12): 1685-93.

[64] WELSH J, MENON H, CHEN D, et al. Pembrolizumab with or without radiation therapy for metastatic non-small cell lung cancer: a randomized phase I/II trial [J]. Journal for ImmunoTherapy of Cancer, 2020, 8(2):

[65] PETERS S, FELIP E, DAFNI U, et al. Safety evaluation of nivolumab added concurrently to radiotherapy in a standard first line chemo-radiotherapy regimen in stage III non-small cell lung cancer—The ETOP NICOLAS trial [J]. Lung Cancer, 2019, 133(83-7.

[66] SHAVERDIAN N, LISBERG A E, BORNAZYAN K, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial [J]. The Lancet Oncology, 2017, 18(7): 895-903.

[67] HWANG W L, NIEMIERKO A, HWANG K L, et al. Clinical Outcomes in Patients With Metastatic Lung Cancer Treated With PD-1/PD-L1 Inhibitors and Thoracic Radiotherapy [J]. JAMA Oncol, 2018, 4(2): 253-5.

[68] TIAN S, SWITCHENKO J M, BUCHWALD Z S, et al. Lung Stereotactic Body Radiation Therapy and Concurrent Immunotherapy: A Multicenter Safety and Toxicity Analysis [J]. Int J Radiat Oncol Biol Phys, 2020, 108(1): 304-13.

[69] LI B, JIANG C, PANG L, et al. Toxicity Profile of Combining PD-1/PD-L1 Inhibitors and Thoracic Radiotherapy in Non-Small Cell Lung Cancer: A Systematic Review [J]. Front Immunol, 2021, 12(627197.

[70] SENAN S, OZGUROGLU M, DANIEL D, et al. Outcomes with durvalumab after chemoradiotherapy in stage IIIA-N2 non-small-cell lung cancer: an exploratory analysis from the PACIFIC trial [J]. ESMO Open, 2022, 7(2): 100410.

[71] BANG A, WILHITE T J, PIKE L R G, et al. Multicenter Evaluation of the Tolerability of Combined Treatment With PD-1 and CTLA-4 Immune Checkpoint Inhibitors and Palliative Radiation Therapy [J]. Int J Radiat Oncol Biol Phys, 2017, 98(2): 344-51.

[72] VON REIBNITZ D, CHAFT J E, WU A J, et al. Safety of combining thoracic radiation therapy with concurrent versus sequential immune checkpoint inhibition [J]. Adv Radiat Oncol, 2018, 3(3): 391-8.