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Rethinking pulmonary toxicity in advanced non-small cell lung cancer in the era of combining anti-PD-1/PD-L1 therapy with thoracic radiotherapy.

Mengqian Li
West China Hospital, Sichuan University

Lu Gan
West China Hospital, Sichuan University

Andrew Song
Thomas Jefferson University

Jianxin Xue
West China Hospital, Sichuan University

You Lu
West China Hospital, Sichuan University

Rethinking Pulmonary Toxicity in Advanced Non-Small Cell Lung Cancer in the era of combining Anti-PD-1/PD-L1 Therapy with Thoracic Radiotherapy

Mengqian Li, Ph.D.[1, #]; Limei Yin, M.D. [1, #]; Andrew Song, M.D.[2, #];
Jianxin Xue, Ph.D.[1, *] and You Lu, M.D. [1]

[1] Department of Thoracic Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China

[2] Department of Radiation Oncology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA

[#] These authors contributed equally.

[*] Corresponding author:
Jianxin Xue, Ph.D., Department of Thoracic Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China. Email: radjianxin@163.com

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Abstract: The combination of programmed cell death 1/programmed cell death ligand 1 blockade and thoracic radiotherapy has become the new standard of care in the treatment of locally advanced non-small-cell lung cancer. The information regarding the pulmonary safety of such therapy remains limited to mostly retrospective studies and case reports with a small portion of data from prospective clinical trials. By analyzing the underlying mechanisms of interactions between radiation and immunotherapy from preclinical data and summarizing safety data from relevant clinical studies with pulmonary toxicity, we believe that longer and rigorous follow-up is warranted, to determine if the combination of such modalities is appropriate for patients without risking undue toxicity.

Key words: thoracic radiotherapy; immunotherapy; non–small cell lung cancer; programmed cell death 1/programmed cell death ligand 1; pneumonitis

Introduction

Programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) immune checkpoint inhibitors (ICIs) are currently one of the most investigated immunotherapies. This blockade has proven its efficacy across various types of tumor including melanoma, Hodgkin`s lymphoma, head and neck cancer, and non-small-cell lung cancer (NSCLC)[1,2]. Objective tumor responses are observed in approximately 40% of PD-L1-positive advanced NSCLC patients, accompanied by significantly increased progression-free survival (PFS) and overall survival (OS) [3-6]. This clinical effect is derived from anti-PD-1/PD-L1 therapy enhancing the antitumor immune response[7]. Radiotherapy facilitates the initial antigen-specific immune responses by inducing inflammatory death of tumor cells, whereby fragmented tumor cells release previously obscured tumor-associated antigens and immune-stimulatory molecules which then trigger an immunogenic response which may elicit an *in-situ* tumor vaccination effect and abscopal effect[8].

Combining radiotherapy with immunotherapy has increasingly become of interest. Multiple preclinical studies demonstrated that thoracic radiotherapy (TRT) can augment the efficacy of anti-PD-1/PD-L1 therapy by priming and recruiting more antitumor effector T cells[9-11]. Recent clinical trials for anti-PD-1/PD-L1 therapy have explored the combination of anti-PD-1/PD-L1 therapy with various cancer therapeutics, including radiotherapy. The combination of anti-PD-1/PD-L1 therapy with TRT in treating locally advanced or metastatic NSCLC has significantly improved PFS and OS when compared with monotherapy, which is demonstrated by the KEYNOTE-001 trial (NCT01295827) (median PFS: 6.3 months *vs.* 2.0 months; median OS: 11.6 months *vs.* 5.3 months) and the PACIFIC study (NCT02125461) (median PFS: 16.8 months *vs.* 5.6 months; median OS: not reached *vs.* 28.7 months)[12-14]. However, with this increased efficacy may come potential increases in toxicity[15,16]. In this review, we will explore the potential toxicity and the underlying mechanisms. Considering the underlying interactions between the two modalities with the currently available evidence, we acknowledge and appreciate the significant efficacy and tremendous promise of the combination of TRT and anti-PD-1/PD-L1 therapy, but have reservations about the view claiming no undue toxicity of this combination therapy[17].

Pulmonary toxicity in anti-PD-1/PD-L1 therapy

Anti-PD-1/PD-L1 monoclonal antibodies (mAbs), is capable of effectively interdicting the immune inhibitory signals mediated by the interaction between PD-1 and PD-L1, which recovers the priming of tumor-antigen-specific T cells and baseline immune response against tumor[7] (Figure 1A).

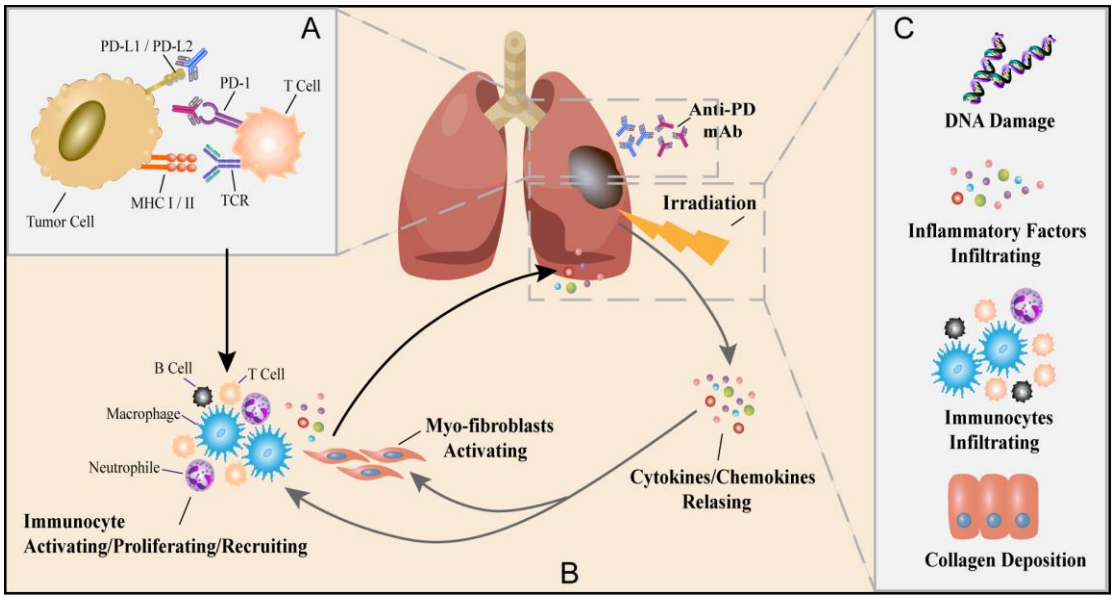

Figure 1. The schematic diagram of combination therapy-induced pulmonary toxicity. (A) PD-1/PD-L1 axis inhibitors are capable of effectively recovering the baseline T-cell immune response against tumor. Inflammatory factors secreted by activated T cells are able to recruit more immunocytes that amplify the anti-tumor effects as well as the pulmonary toxicity. (B) Thoracic radiotherapy generates DNA damage to lung tissue, which contributes to the release of cytokines and chemokines that recruit and activate immunocytes and myo-fibroblasts. (C) The combination of radiotherapy and anti-PD-1/PD-L1 monoclonal antibodies (mAbs) could incur more serious adverse effects relevant to DNA damage, redundant immunocytes infiltrating and inflammatory factors releasing, and collagen deposition.

Unfortunately, PD-1/PD-L1 blockade can cause collateral damage to normal organs and tissues, termed immune-related adverse events (irAEs)[18], i.e. toxicity mediated by antibodies, T cells, and cytokines attacking self-antigens. Anti-PD-1/PD-L1 therapy-related pneumonitis, defined as the inflammation of lung parenchyma, is an indicator of potentially life-threatening irAEs and appears to occur more commonly in patients with lung cancer[19], having resulted in pneumonitis-related deaths observed in several clinical trials[18,20]. Paradoxically, NSCLC patients who received nivolumab and developed irAEs had better OS and longer PFS as compared to those without irAE[21]. The pneumonitis has been reported to occur in 0-10% of the patients receiving anti-PD-1/PD-L1 monotherapy or combination therapy. Delaunay *et al.* unveiled the outcomes of a large-scale retrospective study wherein 1826 cancer patients were treated with ICIs including PD-1 inhibitors, and 3.5% of the patients developed interstitial lung diseases (ILDs)[22]. Fortunately, grade 3 or higher pulmonary adverse events are relatively uncommon in patients.

The underlying etiology and mechanisms of pneumonitis associated with anti-PD-1/PD-L1 mAbs have not been completely determined. One of the potential risk factors for developing irAEs is due to pre-existing autoimmune diseases or subclinical autoimmune syndromes. The PD-1/PD-L1 signaling pathway is an evolutionarily conserved mechanism that maintains self-tolerance mainly through the

inhibition of self-reactive T/B cell responses[23]. Autoimmune conditions can be exacerbated by lowering the threshold for immune activation through checkpoint inhibition[24], resulting in significantly increased risk of irAEs without affecting the therapeutic effects[25]. Another possible mechanism for immune-related pulmonary toxicity is elicited against antigens shared by the tumor and irAE lesions. It has been suggested that pneumonitis observed in patients under PD-1 blockade may be related to the T cells that are similar to the tumor-infiltrating T cells. Moreover, involved T cell clones were also found in the peripheral blood[26], which means any organ with alike antigens may be inflicted by the circulating antigen-specific T cells.

Interestingly, anti-PD-1 mAbs have been associated with a slightly higher incidence of pneumonitis as compared to anti-PD-L1 mAbs (3.6% *vs*. 1.3%), especially regarding to the grade 3–4 pneumonitis (1.1% *vs*. 0.4%)[20]. A meta-analysis estimated that the incidence of any grade pneumonitis among NSCLC patients on anti-PD-1 therapies is 4.1%[18]. One of the possible mechanisms for higher incidence of PD-1-induced pneumonitis lies in the prevention of interaction between PD-L2 and PD-1 by PD-1 blockade. The PD-L2 ligand mainly expresses on DCs, macrophages, Th2 cells and activated T cells. On one hand, Latchman *et al.* identified that both PD-1-PD-L2 and PD-1-PD-L1 signals inhibited the cytokine production and/or cell proliferation of CD4+ T cells by blocking cell cycle progression[27]. On the other hand, PD-1 blockade increases the binding of PD-L2 to repulsive guidance molecule b (RGMb) that expresses in various cancer lines, mouse splenic CD4+ and CD8+ T cells, pulmonary interstitial macrophages, and alveolar epithelial cells, thus leading to vigorous clonal expansion of lung resident T cells and subsequent pneumonitis in the absence of PD-1-mediated tolerance to self-antigens[28]. In addition, a recent study provides evidence of direct interactions between tumor stroma and T cells, showing that reciprocal expression of ligands FASL and PD-L2 was detected in cancer-associated fibroblasts that kill CD8+ T cell via the interaction of PD-L2 with PD-1 and FASL with FAS[29]. Therefore, the absence of interplay between PD-1 and PD-L2 not only promotes the cytokine production and expansion of self-reactive T cells, but also exempts them from being braked and eliminated, which may sharply enhance the anticancer effect as well as the side effects. While PD-L1 blockade could, to an extent, circumvent the restrictions above. This may partially explain the incidence disparity of pulmonary toxicity between PD-1 and PD-L1 blocking[30].

Anti-PD-1/PD-L1 therapy-related pneumonitis can manifest as shortness of breath, cough, fever, or chest pain[19]. Standard of care is guided by clinical symptoms, recommending that mild cases (grade 1–2) are managed with suspending therapy, and higher grade cases with oral or intravenous corticosteroids (grade 2–4), among which severe cases result in hospitalization for intravenous corticosteroids, the permanent cessation of ICIs, and other forms of immunosuppression such as infliximab[31].

Pulmonary toxicity in TRT

Delivery of ionizing radiation to thoracic region in cancer patients, particularly in NSCLC patients, faces a major limitation known as the radiation-induced lung injuries (RILIs), which is thought to be caused by reactive oxygen species produced during the treatment course that leads to DNA damage and subsequent inflammatory responses[32]. Radiation pneumonitis, usually occurring 1–6 months after RT, and pulmonary fibrosis, developing gradually months to years later, are recognized as the acute and late phases in the development of RILI, respectively[33]. Symptoms relevant to RILI are often observed 1–6 months after RT, and may manifest as dyspnea, cough, pyrexia, and mild chest pain. On symptoms progressing, acute respiratory distress inflicted on patients can be life-threatening. RILI is commonly managed with glucocorticoids, supplemental oxygen, as well as antitussive medications if clinically indicated[32].

The primary and optimal strategy to prevent RILI is through rigorous radiation treatment planning to reduce the development of RILI. Treatment plans are generally designed to achieve the percent of total lung volume receiving 20 Gy (V20) ≤ 30-37% and mean lung dose of ≤ 20-21 Gy[33]. Still, RILI cannot be avoided completely even with high-precision TRT. Delineation of clinical target volume and planning target volume requires margins around the tumor in consideration of microscopic diseases, respiratory motion, and setup variability. These margins increase the exposure of benign tissues to high-dose radiation and stimulate an inflammatory and immune reaction[34].

More importantly, disease progression poses a more serious risk than adverse events in patients receiving concurrent chemoradiotherapy. Therefore, adequate therapeutic tumor dose coverage is paramount, and some benign lung tissue will receive TRT for treating lung cancer. Taking the clinical trial RTOG 0617 as an example, a randomized phase III trial of concurrent chemoradiotherapy comparing 74 *vs.* 60 Gy and the use of chemoradiation with or without the addition of cetuximab, reported that without cetuximab the rate of grade ≥ 3 acute pneumonitis was about 5% with 60 Gy and less than 1% with 74 Gy (P = .25), while grade ≥ 3 late pulmonary toxicities (pneumonitis and pulmonary fibrosis) was around 2% in both groups[35]. The secondary analysis of RTOG 0617 comparing intensity-modulated radiation therapy (IMRT) with three-dimensional conformal external beam radiation therapy (3D-CRT) found that IMRT was less likely to induce severe pneumonitis (grade 3 pneumonitis, 3.5% *vs.* 7.9%, P = .039) and improved quality of life[36].

Other factors also known to influence the risk of pneumonitis development include smoking history, preexisting pulmonary function, tumor size and location, heart irradiation dose, select cytokine and glycoprotein levels, the receipt of carboplatin plus paclitaxel chemotherapy in addition to V20, and advanced age[33,37]. Among them, biomarkers, like IL-1α, IL-6, IL-8, sICAM-1, KL-6, CYFRA 21-1, TGF-β1, IP-10, MCP-1 and TIMP-1, are implicated to correlate with higher-grade pulmonary

toxicity[33,38,39]. As an example, TGF-β1, which is activated by RT, facilitates the development and persistence of tissue remodeling and fibrosis in response to irradiation (Figure 1B and 1C). Notably, the production of TGF-β1 by tumor-associated regulatory T cells also has an important role in preventing the development of autoimmunity, which suppresses effector T cells and stimulate the immunosuppressive function of myeloid-derived suppressor cells[40,41].

Pulmonary toxicity with combined radiation and immunotherapy in the pre-clinical and clinical settings

Pre-clinical data

So far, most studies combining ICIs and TRT have suggested an acceptable safety profile in the oligometastatic cancer setting[17]. However, this data lacks robust randomized data. We speculate that the pulmonary toxicity would be increased as compared to a single modality, since the therapies may induce pulmonary toxicity together and could compromise this otherwise promising combination therapy. Briefly, TRT generates oxidative damage to DNA and proteins in lung tissue, causing pulmonary injuries and contributing to the release of tumor antigens and inflammatory factors. After tumor-antigen uptake and processing, antigen-presenting cells migrate to lymphoid organs, and activate naïve T cells therein to become effector T cells. Activated T cells that are further unleashed by anti-PD-1/PD-L1 therapy not only maintain powerful killing effect that may impair normal self-tissues, but can also secrete high-level cytokines that recruit more, even redundant immunocytes into the local regions of the lung. While immunosuppression mechanisms that include myeloid-derived suppressor cells and regulatory T cells are compromised in this setting. Thus, the synergistic interaction of the two treatments sharply amplifies anti-tumor effects, which may also exacerbate the pulmonary toxicity[9,34]. All of these events could magnify serious adverse effects relevant to DNA damage, redundant immunocytes infiltrating and inflammatory factors release, as well as collagen deposition, which goes against the theory of immune normalization that emphasizes the importance of recovering the lost antitumor immunity rather than immune enhancement[2]. (Figure 1C).

Multiple pre-clinical studies have contributed to uncovering the mechanisms underlying the synergistic effect. To name a few examples, tumor antigen-specific interferon-γ produced by effector T cells was substantially enhanced locally by PD-1 blockade in the presence of RT[41]. Remaining to be one of the most important pro-inflammatory cytokines, interferon-γ overexpression is also associated with a number of auto-inflammatory and autoimmune diseases[42], which is reminiscent of the possible mechanisms of irAEs induced by anti-PD-1/PD-L1 therapy that is mentioned above. More specifically, Deng *et al.* demonstrated that combination therapy with IR and PD-L1 blockade optimizes antitumor immunity through enhanced production of T cell-derived tumor necrosis factor (TNF)[9]. TNF-α has been implicated in the pathogenesis of RILI and the induction of TGF-β1[38]. Further, the elevation of plasma

TGF-β1 during radiation therapy predicts radiation-induced pulmonary toxicity, which have been demonstrated in our pre-clinical study[43]. Of note, we also suggested that concurrent anti-PD-1 therapy during TRT could augment pulmonary toxicity and the consequent mortality in the mouse model, where CD8+ T lymphocytes and macrophages with strong positivity for TGF-β1 may have played a key role during the pathological process[11]. Therefore, the upregulation of TNF and TGF-β1 may partially account for the pulmonary toxicity of the combination therapy.

Lastly, a recent perspective by Eric D. and Joe Y. Chang proposed that irradiation of each lesion within multiple tissue beds would fully expose both mutual and exclusive tumor-associated antigens and increase the probability of systemic activation of antitumor immunity better than ICI monotherapy. However, they warned that the safety of multisite comprehensive irradiation has not been routinely analyzed, concerns regarding the toxicities of this approach still remain[44].

Clinical data

Radiotherapy has been thought to be the ideal partner for ICIs[44]. Although there have been several prospective clinical trials combining RT and PD-1/PD-L1 inhibitors (Table 1) started in recent years, most of the trials are still ongoing. Only a small amount of evidence for this combination therapy is available for us at the present moment, and the safety profile appears to be acceptable (Table 2).

Some case reports suggest caution for the diagnosis and management of the toxicity from the combination therapy. Louvel *et al*. reported two cases of six patients treated with concomitant therapy of PD-1/PD-L1 inhibitors and SBRT who developed a radiation pneumonitis[45]. Manapov *et al*. presented that 3 of 25 patients with advanced NSCLC received nivolumab that was initiated as second or third-line therapy several months after TRT developed grade 3 pneumonitis[46]. Yet it was uncertain whether these cases were just related to TRT or if the combination with ICIs played any enhancing role. More interestingly, Shibaki *et al*. presented two cases of nivolumab-induced radiation recall pneumonitis, where two patients with NSCLC received nivolumab treatment 2 years after 60 Gy of TRT developed pneumonitis. The area of nivolumab-induced pneumonitis was consistent with the radiation field in both patients[47]. Although the mechanism of recall pneumonitis is unknown, it seems presumable that nivolumab may have evoked an inflammatory reaction in the patients` previously irradiated fields.

Registration Number	Phases	Tumor Stage	Intervention / Treatment	Arms
NCT03446547	II	I	Durvalumab 1500 mg i.v. every fourth week following SBRT[a].	SBRT *vs*. SBRT + Durvalumab
NCT03383302	I/II	I/II	A flat dose of 240 mg nivolumab infusion will begin after the final fraction of SBRT within 24 hours and subsequently be given every 2 weeks at a flat dose of 240 mg.	SBRT + Nivolumab (adjuvant)
NCT02768558	III	III	Patients will receive 60 Gy of thoracic RT; Cisplatin and Etoposide followed by Nivolumab/Placebo 2 weeks.	Placebo *vs*. CRT[b] + Nivolumab
NCT03245177	I	III, IV	The first dose of pembrolizumab is administered 14 days prior to the initiation of radiotherapy (60-66 Gy in 2 Gy/f, over 40-45 days) and following radiotherapy every 3 weeks thereafter.	RT[c] + Pembrolizumab (concurrent)
NCT02434081	II	III A/B	Four doses of nivolumab 360 mg concurrently with standard chemo-radiotherapy, followed by 480mg from start of nivolumab treatment.	CRT + Nivolumab (concurrent & adjuvant)
NCT03368222	I	III B/ IV	Part A-DOSE LEVEL 1: 200 mg pembrolizumab in week 1 (then 3 weekly) + SBRT dosed at 30 Gy in 3 fractions in week 3. DOSE LEVEL 2: 200 mg pembrolizumab in week 1 (then 3 weekly) + SBRT at 54Gy/ 3f in week 3. Part B-12 patients receive 200 mg of pembrolizumab in week 1 (then 3 weekly) + SBRT in week 3.	RT + Pembrolizumab (concurrent & adjuvant)
NCT02621398	I	II–III B	Beginning 2–6 weeks after, 2 weeks before the end, or at the start of chemotherapy and radiation therapy, patients also receive pembrolizumab.	CRT + Pembrolizumab (concurrent)
NCT03307759	I	IV	SABR[d] followed by pembrolizumab *vs*. Pembrolizumab followed by SABR after cycle 1	SABR + Pembrolizumab (concurrent *vs*. adjuvant)
NCT03158883	I	IV	Avelumab: 10 mg/kg administered q2w. SABR: 50 Gy/5f on every 2 day	SABR + Avelumab (concurrent & adjuvant)
NCT03044626	II	IV	Nivolumab 240 mg fixed dose (q2w). First dose followed by radiotherapy. A metastatic site will be treated with a radiation dose at 20 Gy/5f during a two-week time interval.	SBRT + Nivolumab (concurrent & adjuvant)
NCT02407171	I/II	IV	The starting radiotherapy dose will be 30 Gy/5f and a dose escalation cohort (30Gy/ 3f). MK-3475: 200mg every 2 weeks	SBRT + MK-3475 (concurrent & adjuvant)
NCT02400814	I	IV	Concurrent: MPDL3280A on day 1; SABR begins on day 1 of course 1. Induction: MPDL3280A on day 1; SABR begins on day 1 of course 3. Sequential: SABR begins on day 1 of course 1. After completion of SABR, MPDL3280A IV begins.	SABR + MPDL3280A (concurrent *vs*. adjuvant *vs*. sequential)
NCT03313804	II	IV	Immune checkpoint inhibitor PLUS SBRT	SBRT + Nivolumab/Pembrolizumab /Atezolizumab
NCT03212469	I/II	IV	Durvalumab q4w+ Tremelimumab q4w for up to 4 doses in conjunction with SBRT, then Durvalumab q4w alone for up to 9 additional doses.	SBRT + Durvalumab + Tremelimumab
NCT02444741	I/II	IV	Phase I : Starting dose of Pembrolizumab 100 mg by vein on Day 1 of each 3-week cycle. Phase II : Starting dose of Pembrolizumab at the maximum tolerated dose from Phase I. SBRT delivered at 50 Gy in 4 daily fractions. Wide-field radiation therapy delivered at 45 Gy in 15 daily fractions.	Pembrolizumab + SBRT/ WFRT *vs*. Pembrolizumab

Table 1. Ongoing clinical trials that are testing the effects of combinatorial therapy of programmed cell death 1 (PD-1) /programmed cell death ligand 1 (PD-L1) inhibition and RT in the treatment of lung cancer. SBRT[a]: Stereotactic body radiation therapy; CRT[b]: Chemoradiotherapy; RT[c]: Conventional fractionated radiotherapy; SABR[d]: Stereotactic ablative radiotherapy.

Study	Study Type	Tumor and Stage	Intervention / Treatment	Incidences of Pulmonary Toxicities
Nishino M, *et al.*[18]	Meta-analysis. (Including phase I–III)	Only NSCLC[a] included in this table	PD-1[b] inhibitor monotherapy	All-grade pneumonitis: 4.1%
Khunger M, *et al.*[20]	Meta-analysis. (Including phase I–IV)	NSCLC	PD-1/PD-L1[c] inhibitor monotherapy	All-grade pneumonitis: 3.6% in PD-1 inhibitors, 1.3% in PD-L1 inhibitors
Bradley JD, *et al.* [35]	Prospective study (Phase III)	Stage IIIA/IIIB NSCLC	TRT[d]: 60 Gy *vs*. 74 Gy (without chemotherapy)	All-grade acute pneumonitis: about 9% in the 60 Gy arm, about 11% in the 74 Gy arm All-grade late pneumonitis: about 12% in the 60 Gy arm, 7% in the 74 Gy arm All-grade late pulmonary fibrosis: 10% in the 60 Gy arm, 6% in the 74 Gy arm
Curran WJ, *et al.* [48]	Prospective study (Phase III)	Stage II, IIIA, or IIIB	Chemotherapy + TRT: Arm 1: sequential (63 Gy) Arm 2: concurrent (63 Gy) Arm 3: concurrent (69.6 Gy)	Grade ≥ 3 acute pulmonary toxicities: 9% in arm 1, 3-4% in arm 2 and 3; Grade ≥ 3 late pulmonary toxicities: 14% in arm 1, 13% in arm 2 and 17% in arm 3;
Antonia SJ, *et al.*[12]	Prospective study (Phase III)	Locally advanced NSCC	CRT[e] + Durvalumab	All-grade pneumonitis: 33.9% All-grade pneumonia: 13.1% Grade ≥ 3 pneumonitis: 3.4% Grade ≥ 3 pneumonia: 4.4%
Shaverdian, N, *et al.*[13]	Post hoc analysis	Advanced NSCC	TRT + Pembrolizumab	All-grade pulmonary toxicities: 13%
Peters S, *et al.*[49]	Prospective study (Phase II)	Stage III NSCLC	CRT + Nivolumab	All-grade pneumonitis: 35.4% All-grade Pulmonary fibrosis: 1.7%
Durm, G. A., *et al.*[50]	Prospective study (Phase II)	Stage III NSCLC	CRT + Pembrolizumab	Grade ≥ 2 pneumonitis: 17.2% Grade ≥ 3 pneumonitis: 6.5%
Botticella, A., *et al.*[51]	Retrospective study	NSCLC	TRT+ICIs[f]	All-grade pneumonitis: 16.7% Grade ≥ 3 pneumonitis: 11.1%
Reibnitz, D, *et al.*[52]	Retrospective study	Advanced lung cancer or other tumors with lung metastases	TRT + anti-PD-1/PD-L1 (78%) / anti-CTLA-4 (15%) / anti-PD-1/PD-L1 and anti-CTLA-4 (6%)	Grade ≥ 2 pneumonitis: 6.3% Grade ≥ 2 pneumonia: 17.7%
Hwang WL, *et al.*[17]	Retrospective study	Metastatic NSCLC (95%) and SCLC[g] (5%)	TRT + anti-PD-1/PD-L1	All-grade pneumonitis: 8.2%
Voong KR, *et al.*[53]	Retrospective study	NSCLC	TRT + anti-PD-1/PD-L1	All-grade pneumonitis: 25%
Shibaki R, *et al.*[47]	Case report	NSCLC	TRT + Nivolumab	Two patients with nivolumab-induced radiation recall pneumonitis
Manapov F, *et al.*[46]	Case report	Advanced NSCLC	TRT + Nivolumab	Three patients with grade 3 pneumonitis
Louvel G, *et al.*[45]	Case report	Patient 1: metastatic melanoma Patient 2: metastatic colon cancer	Patient 1: concomitant pembrolizumab + TRT Patient 2: concomitant atezolizumab + TRT	Two patients with radiation pneumonitis

Table 2. Important studies reporting pulmonary toxicity of monotherapy and of the combination of thoracic radiotherapy (TRT) and programmed cell death 1/programmed cell death ligand 1 inhibition. Pneumonitis and pneumonia are both included in the pulmonary toxicity analysis, because differential

diagnosis between pneumonia and pneumonitis relating to immunotherapy or radiotherapy may be clinically challenging. NSCLC[a]: Non-small cell lung cancer; PD-1[b]: programmed cell death 1; PD-L1[c]: programmed cell death ligand 1; TRT[d]: Thoracic radiotherapy; CRT[e]: Chemoradiotherapy; ICIs[f]: immune checkpoint inhibitors; SCLC[g]: Small cell lung cancer

As for retrospective studies, most of them appear to claim that combining PD-1 inhibitors and RT does not result in increased toxicity. Bang *et al.* retrospectively reviewed patients with metastatic NSCLC, melanoma and renal cell cancer, who received CTLA-4 or PD-1 inhibitors and palliative radiotherapy. No relationship between radiation fields and specific irAEs was identified. For instance, 2 in 34 patients (6%) who received TRT and 1 of 79 patients (1%) who did not developed pneumonitis (P = .16)[54]. A retrospective cohort study by Hwang *et al.* included patients with metastatic lung cancer treated with anti-PD-1/PD-L1 therapy. Incidences of all-grade pneumonitis (8.2% *vs.* 5.5%) as well as pneumonitis grade ≥ 2 (4.1% *vs.* 3.3%) were not significantly different between the TRT and non-TRT cohorts[17]. Naidoo *et al.* analyzed patients who received anti-PD-1/PD-L1 mAbs monotherapy or in combination with anti-CTLA-4 mAb, and revealed that most of the patients that developed pneumonitis had not received prior TRT (27 of 43 [63%])[55].

In stark contrast, one study group from Johns Hopkins University retrospectively investigated the role of TRT and the development of immune-related pneumonitis in 184 NSCLC patients who received anti-PD-1/PD-L1 therapy. Anti-PD-1/PD-L1 monotherapy was received in 74% and in combination with other systemic therapy in 26% of the patients. TRT was performed 96 patients (52%). A total of 38 (21%) patients developed pneumonitis, which was more common than that were reported in other clinical trials. Moreover, there was a strong trend towards increased immune-related pneumonitis in patients who underwent TRT compared with those who received other RT (25% *vs.* 9%, P = 0.08)[53]. Together with another retrospective study by the same study group, the overall incidence of checkpoint inhibitor pneumonitis is found to be significantly higher than that was reported in other clinical studies[56]. The retrospective study by Botticella *et al.* also supported that NSCLC patients treated with ICIs and previous curative-intent TRT may be at higher pulmonary risk, where pneumonitis of grade ≥ 3 occurred in 16.7% of the patients on combination therapy and in 2.4% of the patients on ICI monotherapy (P < 0.001)[51]. Possible reasons include increased awareness and pharmacovigilance with irAEs in recent years.

However, limitations of the above retrospective analyses are inherent to the nature of such studies, including incomplete information, lengthy median time between TRT and ICI treatment, and combined analysis of different doses and purposes. Therefore, we should be careful when extrapolating this information.

In the post hoc analysis of the phase I KEYNOTE-001 trial (NCT01295827), all included patients with advanced NSCLC received pembrolizumab and were coded for

having received previous RT (extracranial or thoracic) or not. Significantly prolonged PFS and OS were observed in patients with advanced NSCLC who had received any RT before receiving pembrolizumab than that in patients who did not have. Of note, comparing the 24 patients who received previous TRT and the 73 patients who did not, there was a statistical increase in treatment-related pulmonary toxicities (13% *vs.* 1%, $P = .046$), and a borderline significance was found in the incidence of all pulmonary toxicities (63% *vs.* 40%, $P = .052$), including dyspnea, cough, pneumonitis, and respiratory failure. Although no frequency difference was found in the grade ≥ 3 pulmonary toxicity in both treatment-related pulmonary toxicities and all pulmonary toxicities, RT was implemented at a median of 11.5 months before pembrolizumab treatment[13]. Exposing NSCLC patients to TRT can induce RILI that develop over weeks to months or years[33]. In this study, since TRT was performed several months (median 9.5 months, range 1.0-106.0) prior to ICIs, patients with RILI, especially with severe pneumonitis (grade ≥ 3), may well be excluded from the subsequent ICIs therapy as per the exclusion criteria of most clinical trials. That is, those who received combination therapy were pulmonary function-competent and more likely to withstand the subsequent immunotherapy. In conclusion, KEYNOTE-001 trial can, to some extent, support our perspective that combination therapy augments pulmonary toxicities.

The PACIFIC study (NCT02125461), a prospective, randomized, double-blind, placebo-controlled phase III study enrolled patients with locally advanced NSCLC that had received platinum-based chemotherapy concurrently with definitive radiation therapy (54–66 Gy). Durvalumab, a PD-L1 inhibitor, was administered 1 to 42 days after completion of chemoradiotherapy in the experimental arm, while placebo was administered in the control arm. Pneumonitis of any grade occurred in 33.9% and 24.8% of patients in the durvalumab arm and placebo arm, respectively; grade 3 and 4 occurred in 3.4% and 2.6%, respectively[12]. *P*-values for the pulmonary safety data were not reported. The incidence of grade ≥ 3 pneumonitis in the placebo group was comparable to that in RTOG 9410 (3.4% *vs.* 1–5%)[35]. However, pneumonitis of any grade was more common in both treatment of PACIFIC than that in ATLANTIC study, a durvalumab monotherapy study (33.9% & 24.8% *vs.* ≤ 3%)[57]. This variability may be attributed to the requirement for prior TRT in PACIFIC, which could have predisposed patients to pulmonary adverse events, a hint for the role of TRT in increasing pulmonary side effects[58]. Symptoms such as cough (35.4% *vs.* 25.2%), dyspnea (22.3% *vs.* 23.9%) and pyrexia (14.7% *vs.* 9.0%), which are possibly relevant to RILI and have been included in KEYNOTE-001 trial and other studies[19], were not included in the pulmonary toxicity analysis of this study. Additionally, differentiating between pulmonary infection (pneumonia in both arms: 13.1% *vs.* 7.7%) and pneumonitis relating to immunotherapy or radiotherapy may be clinically challenging[59,60]. Hence, we conjecture that the authentic incidence of pulmonary toxicity has been underrated because of the exclusion of other respiratory symptoms and pneumonia from pulmonary toxicity analysis.

Another multicenter single-arm phase II study spearheaded by Indiana University adopting the same treatment mode as the PACIFIC study reported the incidence of grade ≥ 3 pneumonitis at 6.5%, which is the double of the PACIFIC study[50]. However, only 43.5% of patients completed the one-year adjuvant immunotherapy and 19.6% failed due to adverse events, suggesting the incomplete information of pneumonitis incidence on combination therapy. Of note, 75% cases of grade ≥2 pneumonitis occurred within the first 12 weeks after pembrolizumab treatment[50]. Similarly, with TRT and immunotherapy being prescribed sequentially rather than concurrently, the report of the second primary endpoint for PACIFIC study revealed that time < 14 days from prior RT to randomization witnessed quite different proportions of any-grade pneumonitis (39.2% *vs*. 16.7%, without the *P*-value reported) in the durvalumab arm and placebo arm[61].which is reminiscent of concurrent combination therapy that is more likely to prime a stronger immune response[44] as well as worsen the pulmonary toxicity in the light of published preclinical evidence from concurrent irradiation and PD-1 blockade in increasing cardiac toxicity[62,63]. The safety data from NICOLAS (NCT02434081) study, to some extent, corroborates our speculation. This is a single-arm study evaluating the safety of combining nivolumab with the first-line chemo-TRT (≥ 60 Gy) regimen in stage III NSCLC. Pneumonitis of any grade occurred in 32.7% of the evaluated 58 patients, with grade 1/2 and 3 making up 22.4% and 10.3%, respectively. Pneumonitis of grade ≥ 3 is remarkably increased as compared to studies above, while the remaining respiratory disorders, including dyspnea (20.7%), cough (31.0%), pulmonary fibrosis (1.7%) and respiratory insufficiency (1.7%), are comparable to other studies[49].

Real-World Toxicities Higher Than in Trials

Even if prospective clinical trials, such as the PACIFIC study, have offered more objective and reliable evidence as compared with retrospective studies, their results may still not reflect the real-world data. For instance, patients with history of interstitial lung disease (ILD) were routinely excluded from the clinical trials studying the combination of ICIs and TRT. In fact, the incidence of lung cancer is high in patients with idiopathic pulmonary fibrosis (25.2 cases per 1000 person-years), a specific form of ILD of unknown cause[64]. NSCLC patients who were treated with SBRT, the cumulative incidences of radiation pneumonitis worse than grade 2 (55.0% *vs.*13.3%, $P < .001$) and worse than grade 3 were significantly higher in ILD (+) group than those in ILD (−) group (10.0% *vs.* 1.5%; $P = .02$)[65]. Furthermore, referring to the instructions of anti-PD-1/PD-L1 mAbs, in the case of grade 2 or higher-grade immune-mediated pneumonitis or ILD, withholding immunotherapy is emphasized. Collectively, patients with ILD are more prone to pulmonary toxicities by TRT, ICIs, or more possibly by the combination therapy. The exclusion of this patient group could artificially reduce the incidence of combination therapy-related pneumonitis. Additionally, with the improvement of medical technology and our ability to diagnose irAEs, rates are increasing as observed at the population level[56].

Conclusion

Since most irAEs are treatable, recognizing these events earlier on could improve quality of life of patients. Our purpose is to promote awareness amongst medical oncologists, radiation oncologists, pulmonologists, emergency physicians, and other medical providers to have a high index of suspicion of potential pulmonary toxicity from the combination of radiation therapy with immunotherapy in the setting of advanced NSCLC. Most of the available data suggests that combining radiation and immune checkpoint blockade are generally safe, but more data with longer and rigorous follow-up are needed. Whether such a treatment course is appropriate for patients without risking undue toxicity from co-administration is left unanswered at this time. The information presented above presents a potential trend towards increased incidence of immune-related, radiation pneumonitis in patients on combination therapy. Therefore, we are cautiously optimistic and recommend attention to monitoring for pneumonitis in patients with NSCLC during combination therapy, particularly with anti-PD-1/PD-L1 inhibitors.

Author Contributions

Xue JX and Lu Y: conceived the idea for the manuscript. Li MQ and Yin LM: collected information and wrote the manuscript. Song A: provided critical analysis and language editing. All authors contributed to the writing and final approval of the manuscript.

Conflict of Interest

We have no conflicts of interest to declare.

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2. Part of the materials used in the Figure 1 was downloaded from https://www.flaticon.com/, https://reactome.org/ and https://www.vecteezy.com/.

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