The efficacy and safety of immune checkpoints inhibitors plus radiotherapy as a combination therapy for advanced non-small cell lung carcinoma: a meta-analysis

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Abstract

Background

Immune checkpoint inhibitors have showed good efficacy in advanced non-small-cell lung cancer(NSCLC). This meta-analysis was conducted to explore the therapeutic efficacy and safety of immune checkpoint inhibitors combined with radiotherapy for patients with advanced NSCLC.

Methods

We used many proper keywords to perform a systematic search in databases and performed a meta-analysis of trials that conducted immune checkpoint inhibitors plus radiotherapy as a treatment for advanced non-small-cell lung cancer. The outcomes included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and treatment-related adverse events. A fixed-effect or random-effects model was adopted depending on between-study heterogeneity.

Results

Ten trials were finally included in this meta-analysis. The combined ORR and DCR was 34% (19%-49%) and 72% (65%-79%). The combined six-month progression-free survival rates (PFSR6m) and one-year overall survival rate(OSR1y) were 50.0% (29.4%-72.8%) and 59.0% (48%-69%). Immune checkpoint inhibitors plus radiotherapy was significantly associated with improvement of PFS (hazards ratio [HR], 0.64; 95% CI 0.46–0.90; P = 0.01), OS (HR, 0.62; 95% CI 0.46–0.85; P = 0.003). In subgroup analyses, the combined ORR was 31.5% (16.4%-46.6%), combined DCR was 72.1% (63.3%-80.9%), combined PFS6m was 50.0% (20.6%-79.5%) and combined OSR1y was 59.7% (48.1%-71.2%) for anti-PD-1/PD-L1 antibody plus radiotherapy. The combined ORR was 19.5% (9.1%-29.8%) for anti-CTLA4 antibody plus radiotherapy. The combined PFS6m and OSR1y were 58.9% (26.2%-91.7%) and 59.7% (29.7%-89.8%) respectively for the concurrent therapy group. And the combined PFS6m and OS1y were 55.2% (41.6%-68.8%) and 55.7% (42.1%-69.3%) for sequential therapy. For the low-dose radiotherapy group. The combined PFS6m and OS1y were 45.9% (27.0%-64.8%) and 51.6% (37.5%-65.6%). The combined PFS6m and OS1y were 71.1% (37.9%-104.4%) and 67.4% (29.2%-105.6%) separately for high-dose radiotherapy group. When using as first-line therapy. The combined ORR was 53.8% (23.6%-84.1%) and combined ORR was 76.5% (65.0%-88.1%). While as subsequent therapy, the combined ORR and DCR were 25.9% (14.7%-37.2%) and 69.9% (60.9%-78.9%). The combined PFS6m and OS1y were 51.1% (40.3%-61.9%) and 51.8% (40.9%-62.7%).

Conclusions

Immune checkpoint inhibitors plus radiotherapy might be an effective and tolerable option as a treatment for advanced NSCLC.

Background

Lung cancer is still a worldwide healthy problem, leading the highest mortality for both male and female^[1]. In China, the data from cancer statistics showed that there were 733,000 newly diagnosed lung cancer cases and 60 million lung cancer deaths in 2015^[2]. NSCLC took the most proportion in all types of lung cancer, about 85–90%^[3]. Unfortunately, most patients were at advanced stage when diagnosed, no chance of healing^[4]. These patients had to rely on systemic therapy. In which, the traditional platinum-based chemotherapy was the most important treatment in a very long period. But the survival time was unsatisfactory for its efficacy was limited and its toxic side's effect was remarkably^[5]. A significant improvement has been achieved by gene-driven targeted therapy, including epidermal growth factor receptor (EGFR)-Tyrosine Kinase Inhibitor (TKI), inhibitor of anaplastic lymphoma kinase (ALK) and ROS proto-oncogene 1 receptor tyrosine kinase (ROS1). The gene-driven targeted therapy was reported a much higher response rate for patients with relative gene-driven mutation^[6–8]. Moreover, it reveals Chinese patients gained more benefits because of a higher mutation rate in EGFR^[9]. However, for patients without relative gene-driven mutation, there was still no better choice of treatment.

Until the past decades, the appearance of immune checkpoint inhibitors (ICIs) was an inspiring breakthrough in lung cancer treatment. Actually, scholars has begun their researches into immunotherapy for really a long time. Theoretically, cancer cells can be recognized as “non-self” by the host immune system though the new antigens they generated. However, there are many reported mechanisms for them to escape from the anti-tumor immunity, such as down-regulation the antigen-presenting, immunoediting, induction of self-tolerance and up-regulation of immune checkpoints in the tumor micro-environment^[10]. Many researches have been carried out, aiming to find an effective immunotherapy for cancer patients. At first, researchers focused on anti-cancer vaccines and nonspecific immune stimulants, which did not reveal significant effect^[11–12]. Then they start to put an eye on targeting negative regulators of the immune system, which showed significant anti-tumor activity in many types of solid tumors^[13]. Up to now, two major pathways have came under observation in metastatic NSCLC, corresponding to two relevant immune checkpoints. The first one is cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). CTLA-4 is a CD28 homolog which is only expressed on T cells^[14]. It can bind B7 to format CTLA-4:B7 binding though competing with CD28, resulting in a negative signal to inhibit the production IL-2 and cell cycle progression so that to prevent the activation of T cell^[15]. It was proved CTLA-4 blockade could enhance anti-tumor response in some preclinical studies^[16]. And positive results has been achieved in clinical trials. The most representative drugs are ipilimumab and tremelimumab^[17–19]. The other immune checkpoint is programmed cell death protein-1 (PD-1), which is expressed on the surface of activated T cells, B cells and natural killer cells^[20]. PD-1 can recognize two known ligands, programmed cell death ligand-1 (PD-L1) and programmed cell death ligand-2 (PD-L2), to down-regulates the effectiveness of T cells. And PD-L1 was found to express on surface of various kinds of cells including the T cells. Moreover, it was also found over-expressed on tumor cells^[21]. The results of preclinical studies have showed the PD-1 and PD-L1 blockade could inhibit tumor growth, which provided the evidence for clinical trials^[22]. Up to now, there are many PD-1/PD-L1 inhibitors being proved their efficacy in treating NSCLC, including nivolumab^[23], pembrolizumab^[24], and atezolizumab^[25].

Though immunotherapy have dramatically changed the treatment patterns of NSCLC patients, not all NSCLC patients have gained the survival benefit. Also they had to face the same drug-resistance problem. Hence, the researchers begun to explore combination therapy. The first one try is the ICIs combined with chemotherapy. L. Gandhi etc has demonstrated a better overall survival and progression-free survival for NSCLC patients without EGFR or ALK mutations by treating pembrolizumab combined platinum-based drug as first line therapy^[26]. This synergistic effect was also proved in some other studies^[27–28], which provided a new treatment strategy for NSCLC patients. For the different timing working on T cells and different locations between CTLA-4 and PD-1, researchers also tried a combination treatment with CTLA-4 and PD-1 inhibitors, which is a research hotspot recently. Some studies have showed nivolumab plus ipilimumab could result in a longer overall survival than chemotherapy in patients with advanced or recurrent NSCLC^[29]. Moreover, researches on the ICIs combination with EGFR-TKIs or antiangiogenic agents are ongoing too^[30–32].

Besides, researchers are also studying on the combination of ICIs with radiotherapy (RT) for its immunomodulatory effect has been found. And many researches have being carried out to explore the potential mechanisms, which as follows: inducing immune responses^[33], killing the immunogenic cells which will release tumor antigens^[34], activating the “stimulator of interferon genes” to generate an adequate immune response^[35], improving the ability of tumor cell recognition^[36]. Moreover, the more pronounced tumor regression by combination of ICIs and RT has been proved by several preclinical studies^[37–39], which strengthens the hypothesis that RT can be an immunomodulatory in combination with immunotherapy. The results of Antonia SJ etc’s study has showed that durvalumab, as consolidation immunotherapy after concurrent platinum-based chemoradiation for unresectable stage III NSCLC patients, resulted in significantly longer overall survival than placebo^[40]. But for advanced NSCLC patients, there is still controversy about the efficacy, safety and timing of combination of RT with ICIs. Therefore, our meta-analysis is trying to explore these questions.

Patents And Method

Search strategy and study selection

We used free-text words and MeSH terms to do the research. Two investigators (Dan Yang and LuLu Wang) independently searched for studies that published in English from PubMed, SpringerLink, Embase, Web of Science, Medline, and the Cochrane Library, using the keywords including pembrolizumab or nivolumab or atezolizumab or durvalumab or ipilimumab or PD-1 or PD-L1 or CTLA-4 or ICIs, RT and non-small cell lung cancer. The last search was performed on June 1, 2020. We also performed the reviewed abstracts from major conference proceedings of a computerized search of American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO), and the American Association for Cancer Research (AACR), the European Lung Cancer Conference (ELCC) and the World Conference on Lung Cancer (WCLC). We only included the most complete and updated data of the study.

The inclusion criteria were below: (i) the study reported using ICIs plus non-traditional RT in advanced lung cancer patients; (ii) any of the following measurements were investigated: response rate (RR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS); (iii) the study was a clinical trial published in English.

The following exclusion criteria were used: (i) case reports, editorials, letters, expert opinions, or reviews; (ii) studies don’t publish any related data; (iii) repeated publications.

Data extraction and quality assessment

Two authors (Dan Yang and LuLu Wang) independently extracted the data. Any discrepancies were resolved by consensus. The following information was extracted from each study: first author, number of patients, randomization, trial phase, year of publication or conference presentation, clinical characteristics of enrolled patients including PD-L1 level, ICIs drug, the timing and dose of RT, follow-up information, treatment outcomes including RR, DCR, PFS, OS, six-month PFS rate (PFSR6m), or one-year OS rate (OSR1y) and treatment-related adverse events (AEs).

The I² statistic was used to evaluate the heterogeneity between studies. It was considered significant heterogeneity If I² > 50%. An effect model by Mantel-Haenszel was used if heterogeneity was observed and subgroup analysis was performed to reduce heterogeneity^[41]. Possible publication bias was detected by funnel plots. To assess the stability of combined results by excluding studies one by one, sensitivity analysis was performed. Most analyses were performed using STATA version 16.0 (Stata Corporation, College Station, TX).

Quality control

We used the Cochrane Collaboration’s tool to conduct the risk of bias assessment of the random trails. We used the Newcastle Ottawa Scale (NOS) to evaluate the quality of enrolled single-arm or non-controlled studies^[42]. Studies were divided into three grades: poor, modest, and high quality, according to scores ranging from 0 to 3, 4 to 6, and 7 to 9, respectively.

Results

Literature search

The flow diagram for study inclusion is revealed in Figure 1. The preliminary literature search identified 683 abstracts, and 673 papers from databases that fulfilled our inclusion criteria. Titles and abstracts were reviewed, and 331 potential full-text articles were evaluated for eligibility. All relevant references were reviewed. Ten clinical trials were finally identified for inclusion in our study, including 7 non-randomized trials and 3 randomized trials.

Seven of these 10 studies reported the efficacy of anti-PD-1/PD-L1 antibodies plus RT in the treatment of advanced lung cancer, two investigated the efficacy of CTLA4 antibody plus RT, and one investigated the efficacy of anti-PD-1/PD-L1 antibodies plus CTLA4 antibody plus RT.

Study characteristics

Four of the studies were two-armed while the rest six studies without a control group. Most trials were phase 1/2 studies. In total, 3995 patients were enrolled in this meta-analysis. All studies were from 5 different countries, most of them were from USA; the rest were from France, Italy, Spain, and Netherlands separately. Most of the patients had a PS of 0–1. The median follow-up ranged from 7.3 to 23.6 months.

Seven of the ten researches provided data to extract the overall response rate (ORR) while six were available to extract the DCR. Meanwhile, seven studies were available to extract the OS1y and six studies were available to determine the PFS6m. Details of the study characteristics are showed in Table 1.

Main analysis

We assessed the efficacy of combination regimens of ICIs and RT separately according to the data they provided (Figure 2). The combined ORR and DCR was 34 % (95% CI: 19%-49%) and 72 % (95% CI: 65%-79%) separately. The combined PFS6m and OS1y values were 50.0% (29.4%-72.8%) and 59.0% (48%-69%), respectively. The fixed-effect model was used for DCR while the random-effect model was used for the other three analyses because of the significant heterogeneity.

Among the four two-armed studies, three studies provided the ORR and OS1y of the control groups, while only two studies provided the DCR and PFS6m. The combined ORR and DCR was 25 % (95% CI: 16%-34%) and 52 % (95% CI: 39%-64%) separately. The combined PFS6m and OS1y values were 35% (23%-47%) and 41.0% (23%-60%), respectively. The random-effect model was used to access the OS1y values because of the significant heterogeneity ($I^2=0.853$).

Subgroup analyses

To investigate possible reasons for the heterogeneity, we performed subgroup analyses according to whether the trial was two-armed, whether the trial was prospective, the different types of ICIs, the different line of treatment, the different timing of RT.

Five studies were two-armed studies. But only two studies provided HR values of PFS while three studies provided HR values of OS. The combined HR and its 95% CI for PFS of the two studies was 0.64 (0.46-0.90), with statistical significance ($z=2.55$, $p=0.01$). This result indicates that ICIs combined with RT led to a significant improvement in PFS compared with ICIs alone in advanced NSCLC. Meanwhile, the combined HR and its 95% CI for OS of the three studies was 0.62 (0.46-0.85), with statistical significance ($z=2.99$, $p=0.003$). This result also indicates that ICIs combined with RT led to a significant improvement in OS, comparing with ICIs alone in advanced NSCLC. A forest plot is shown in Figure 3.

Seven studies were prospective studies, and all these studies have provided the ORR of the combination therapy group. The combined ORR was 33.9% [18.6%-49.3%] with significant heterogeneity (Q statistic, 34.75; I^2 , 82.7%; $p=0.000$). A random-effect model was performed. Six studies have provided the DCR and the combined DCR was 72.4% [65.3%-79.5%] with good heterogeneity (Q statistic, 3.24; I^2 , 0.0%; $p=0.663$). A fixed-effect model was performed. Four studies have provided the PFS6m and OS1y of the combination therapy group. The combined PFS6m and OS1y was 50.5% [25.0%-76.0%] and 58.9% [38.5%-79.4%] respectively, with significant heterogeneity. A random-effect model was performed.

Six studies investigated the efficacy of an anti-PD-1/PD-L1 antibody combined with RT. Four studies provided the ORR and DCR of the study groups. The combined ORR was 31.5% [16.4%-46.6%] with significant heterogeneity (Q statistic, 7.86; I^2 , 61.8%; $p=0.049$). A random-effect model was performed. The combined DCR was 72.1 % (63.3%-80.9%) with good significant heterogeneity (Q statistic, 3.17; I^2 , 5.5%; $p=0.366$). A fixed-effect model was performed. Five studies provided the PFS6m of the study groups. The combined PFS6m was 50.0% [20.6%-79.5%] with significant heterogeneity (Q statistic, 67.57; I^2 , 94.1%; $p=0.000$). A random-effect model was performed. Six studies provided the OS1y of the study groups. The combined OS1y was 59.7% [48.1%-71.2%] with significant heterogeneity (Q statistic, 20.47; I^2 , 75.6%; $p=0.001$). A random-effect model was performed. Only two studies investigated the efficacy of an anti-CTLA4 antibody combined with RT and only provided the ORR of the combination treatment group. The combined ORR was 19.5 % (9.1%-29.8%) with good significant heterogeneity (Q statistic, 0.26; I^2 , 0.0%; $p=0.612$). A fixed-effect model was performed.

We divided these trials into two subgroups according to the timing of RT. One is the concurrent therapy group, in which patients received RT at the first dose of ICIs or after the first dose. The other one is the sequential group, in which patients received the first dose of ICIs after the completion of RT. There are five studies in the concurrent therapy group. All five studies provided the ORR and the combined ORR was 21.3% [13.9%-28.6%] with good heterogeneity (Q statistic, 2.37; I^2 , 0.0%; $p=0.669$). A fixed-effect model was performed. Four studies provide the DCR and the combined DCR was 71.8% [62.0%-81.6%] with good heterogeneity (Q statistic, 3.18; I^2 , 5.7%; $p=0.365$). A fixed-effect model was performed. Three studies have provided the PFS6m and OS1y of the concurrent therapy group. The combined PFS6m and OS1y were 58.9% [26.2%-91.7%] and 59.7% [29.7%-89.8%] respectively, with significant heterogeneity. A random-effect model was performed. Meanwhile, only two studies investigated the efficacy of sequential therapy. According to the data provided, we can only do the combination of PFS6m and OS1y. The results were 55.2% [41.6%-68.8%] and 55.7% [42.1%-69.3%] respectively, with good heterogeneity (Q statistic, 0.21; I^2 , 0.0%; $p=0.649$). A fixed-effect model was performed.

Among all the enrolled studies, the total dose and fractionation of RT significantly differed. We defined a low-dose group when RT dose <45Gy, and a high-dose group if RT dose $\geq$ 45Gy. Three studies investigated the efficacy of combination with low-dose RT. All three studies provided the ORR and the DCR of the study groups. The combined ORR was 30.2% [10.7%-49.6%] with significant heterogeneity (Q statistic, 7.47; I^2 , 73.2%; $p=0.024$). A random-effect model was performed. The combined DCR was 69.7% [59.8%-79.6%] with good heterogeneity (Q statistic, 2.12; I^2 , 5.9%; $p=0.346$). A fixed-effect model was performed. Two studies have provided the PFS6m and OS1y of the low-dose RT therapy group. The combined PFS6m was 45.9% [27.0%-64.8%] with modestly significant heterogeneity (Q statistic, 1.6; I^2 , 37.3%; $p=0.207$). A random-effect model was performed. The combined OS1y was 51.6% [37.5%-65.6%] with good

heterogeneity (Q statistic, 0.61; I², 0.0%; p = 0.436). A fixed-effect model was performed. Three studies investigated the efficacy of combination with high-dose RT. All three studies provided the ORR of the study groups. The combined ORR was 22.3% [12.8%–31.8%] with good heterogeneity (Q statistic, 2.02; I², 1.2%; p = 0.363). A fixed-effect model was performed. Two studies provided the DCR of the study groups. The combined DCR was 76.6% [62.2%–90.9%] with good heterogeneity (Q statistic, 0.46; I², 0.0%; p = 0.498). A fixed-effect model was performed. Two studies have provided the PFS6m and OS1y. The combined PFS6m and OS1y were 71.1% [37.9%–104.4%] and 67.4% [29.2%–105.6%] separately, with significant heterogeneity. A random-effect model was performed.

Patients in three studies received the combination therapy as first-line therapy. Two studies provided the ORR and the DCR of the study groups. The combined ORR was 53.8% [23.6%–84.1%] with significant heterogeneity (Q statistic, 4.62; I², 78.4%; p = 0.032). A random-effect model was performed. The combined DCR was 76.5% [65.0%–88.1%] with good heterogeneity (Q statistic, 0.32; I², 0.0%; p = 0.569). A fixed-effect model was performed. Patients in other six studies received the combination therapy as at least second-line therapy. Five studies provided the ORR of the study groups. The combined ORR was 25.9% [14.7%–37.2%] with modestly significant heterogeneity (Q statistic, 9.48; I², 57.8%; p = 0.050). A random-effect model was performed. Four studies provided the DCR of the study groups. The combined DCR was 69.9% [60.9%–78.9%] with good heterogeneity (Q statistic, 2.14; I², 0.0%; p = 0.545). A fixed-effect model was performed. Four studies have provided the PFS6m and OS1y of the combination group. The combined PFS6m and OS1y were 51.1% [40.3%–61.9%] and 51.8% [40.9%–62.7%] respectively, both with good heterogeneity. A fixed-effect model was performed.

Tolerability

Generally speaking, sides' effects were tolerable. The most commonly reported treatment-related AEs of 3/4 grade for the combination of ICIs and RT were endocrinological toxicities, asthenia, hematological toxicities, pneumonitis, and dermatological toxicities.

Sensitivity analysis and publication bias

We performed sensitivity analysis to detect the robustness of the combined outcomes. Omitting any single trial did not significantly alter the results. We also used a funnel plot to observe the potential of publication bias for the ORR, DCR, PFS6m and OS1y of the ICIs plus RT therapy in NSCLC patients. The possible reason might be the limit number of trials.

Discussion

In recent years, several ICIs medicines, including anti-PD-1/PD-L1 antibody and anti-CTLA4 antibody, have been improved good efficacy in NSCLC patients [18–19, 23–25]. In order to get better efficacy, combination therapy have been proposed, such as ICIs plus chemotherapy, ICIs plus target therapy, anti-PD-1/PD-L1 antibody plus anti-CTLA4 antibody and ICIs plus RT. For patients with unresectable stage III NSCLC, durvalumab has showed its advantage to improve their OS and PFS, as maintenance therapy after concurrent chemoradiation [40]. However, for patients with advanced NSCLC, the efficacy of ICIs plus RT is still uncertain. So we performed this meta-analysis to investigate potential therapy strategies for advanced NSCLC patients.

ICIs were an inspiring breakthrough in cancer therapy in recent years. The ORR of single therapy ranged from 19.4–20%, and the OS1y ranged from 42%–47.9% [19, 24–25]. From our results, the combined ORR of ICIs plus RT is 34%, and the OS1y is 59%, which revealed an impressive efficacy of the combination therapy with tolerable side effects. This result was consistent with many preclinical studies, which showed RT could cause the immunomodulatory effect to prove the more pronounced tumor regression by combination with ICIs [33–39]. Moreover, our results showed a significant improvement in both PFS (%95 CI: 0.46–0.90 p = 0.01) and OS (%95 CI: 0.46–0.85 p = 0.003) for the combination therapy of ICIs plus RT comparing with the single ICIs therapy, which revealed the combination therapy might be a better therapy strategy for advanced NSCLC. But in our study there are only two two-armed trials providing the HR values of PFS and three trials providing the HR values of OS. More prospective trials are ongoing now. Therefore, further study is needed to verify this outcome.

As we said before, there are two types of ICIs widely being used in clinical treatment for NSCLC. They are anti-PD-1/PD-L1 antibody and anti-CTLA4 antibody. From previous report, the ORR for anti-PD-1/PD-L1 antibody and anti-CTLA4 antibody single treatment were 20% and 4.8% respectively. In our study, the results showed that combined ORR were 31.5% and 19.5% respectively, which revealed that the combination with RT could sharply improve the efficacy for both anti-PD-1/PD-L1 antibody and anti-CTLA4 antibody. But the efficacy was different between them, the ORR of anti-PD-1/PD-L1 antibody plus RT was higher than anti-CTLA4 antibody plus RT, which was accordant with the results when they were used as single therapy treating patients with melanoma [53]. This might because though both anti-PD-1/PD-L1 antibody and anti-CTLA4 antibody showed the efficacy on treating cancers, but for the difference of their responsible signaling mechanisms and their ligands' location, they also differed on the efficacy on anti-tumors. This theory also provided another way of combination therapy of anti-PD-1/PD-L1 antibody plus anti-CTLA4 antibody plus RT. The only included trial (NCT03223155), exploring the efficacy of anti-PD-1/PD-L1 antibody plus anti-CTLA4 antibody plus RT, is a prospective trial, which is still ongoing. The preliminary result showed a really good result of ORR (68%), which is much higher than double medicine combination. We will pay close attention to the final result and will also concern about the tolerance of patients.

As for the timing of RT when combined with ICIs, the best strategy is still uncertain. Like we said before, inducing immune responses is one potential mechanisms for RT to enhance the efficacy of ICIs. This was reported to be achieved by the increase of cell surface–MHC class I expression, which can be test just 18 h after RT [36]. On the other hand, it was also observed that the PD-L1 expression was significantly increased after RT, which might reveal a worse response to RT in NSCLC [38]. Through down regulating PD-L1 expression, the percentage of apoptotic cells was significantly increased after radiation than that in the cells without radiation. So that the radiation resistance was alleviated. Moreover, the combination of anti-PD-1/PD-L1 antibody and RT could reduce the accumulation of MDSCs, which has also been demonstrated to be relative with radiation resistance [54]. Therefore, we can conclude that the anti-PD-1/PD-L1 antibody may also improve the efficacy of RT by blockade of PD-L1. Taken together, it seems that concurrent ICIs and RT would have better efficacy than sequential therapy, because ICIs and RT can enhance each other's effectiveness. But our results did not show any significant difference on the combined PFS6m and OS1y between these two types of combination strategies. However, the number of enrolled studies for sequential therapy is limited, which might

affect the result. And in the PEMBRO-RT trial, which was a random prospective study for sequential therapy, the first course of ICIs was given within 7 days after completion of RT. Though it was included in the sequential therapy group, there was not a long interval time between ICIs and RT. After all, the best timing for the combination of ICIs and RT still need more prospective study for further confirm.

Another uncertain problem is the dose of RT when combined with ICIs. The result of Eric A. Refits' study showed that the increase of cell surface-MHC class I expression after radiation was dose dependent [36]. Moreover, the increase of PD-L1 expression after radiation was also reported to be dose relative [38]. We hypothesized the dose of RT might also affect the efficacy of combination therapy. Since, we analyzed the efficacy of low-dose RT group and high-dose RT group separately. The results showed that the low-dose group had a better ORR. But the PFS6m (71.1% vs 45.9%) and OS1y (67.4% vs 51.6%) of high-dose group were much higher, which seemed to confirm our hypothesis. For the high-dose RT might accompany with higher incidence of side effects, the best total dose remains uncertain. The dose fractionation might be another factor to affect the results. But we could not analyze the efficacy of different ways of dose fractionation, for it differed in different studies and even in the same study it was not uniform. So more prospective studies to explore the dose and the fraction strategy are needed.

In our studies, most trials investigated ICIs plus RT as subsequent therapy in advanced NSCLC. The results showed the combined ORR was 25.9%, PFS6m was 51.1% and OS1y was 51.8%, while they were reported 18–20%, 28.1–35.5% and 42–51% separately for single ICIs treatment as subsequent therapy [23, 24, 55]. It seems that the combined therapy lead to a better ORR and PFS, but the similar OS. In our study, NCT02444741 is the only prospective study investigating ICIs plus RT as first-line treatment. Their results did not show significant difference between two groups not only in RR (22% vs 25%, $P = 1.00$), but also in PFS (10.9 vs 8.4 months, $p = 0.83$). As for the non-traditional fractionation group, which was more concerned in our study, it showed a much better ORR (38%) and a longer PFS (21.1 months). For the elementary data of this trial was just published in the conference report, more data was expected.

Although just few studies were enrolled in our meta-analysis, this is the first meta-analysis to evaluate the efficacy and safety of the combination of ICIs plus RT as treatment strategies in advanced NSCLC. To minimize the influence of heterogeneity, we used the random-effects model and performed exploratory subgroup analyses based on whether the trial was two-armed, whether the trial was prospective, the different types of ICIs, the different lines of treatment and the different timing of RT.

However, our meta-analysis had several limitations. Firstly, most of the studies just had small sample sizes because studies focusing on ICIs plus RT for advanced NSCLC are not much. Secondly, most trails only involved single-arm studies without randomization. Thirdly, most trails did not define the exact the dose fractionation and timing of RT. Fourthly, we widely use the random-effects model in our analysis, which may increase the effects of small samples with poor quality studies. Finally a potential impact of publication bias and selection bias might existed. These limitations may have affected the final results.

In our study, the data are insufficient, but various trials are still ongoing. Some more single-armed trials are investigating the efficacy and safety of ICIs plus RT, including NCT03557411, NCT03812549 and NCT03705806. There are also more trials are comparing the efficacy between ICIs plus RT and ICIs, including NCT03774732, NCT03867175 and NCT02658097. The antitumor effect of PD-1/PD-L1 antibody plus CTLA4 antibody on NSCLC was proved. The efficacy of double checkpoint inhibitors in lung cancer plus RT is being evaluated in one ongoing trial (NCT03275597). Moreover the combination of ICIs plus RT is also evaluated as neoadjuvant therapy in one ongoing trail (NCT04245514). And this trial also is investigating the best RT fractionation for combination therapy. These results will elucidate the efficacy of ICIs plus RT.

Conclusions

Our meta-analysis suggests that combination treatment with ICIs plus RT is an effective and tolerable option as a treatment for advanced NSCLC. Further prospective, multicenter, randomized control trials are urgently needed to validate our results. The location, dose and fractionation of RT should be considered in the design of future studies. The costs of these strategies together with patients'quality of life should also be carefully evaluated.

Abbreviations

NSCLC, non-small-cell lung cancer; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; PFSR6m, six-month progression-free survival rates; OSR1y, one-year overall survival rate; HR, hazards ratio; EGFR, epidermal growth factor receptor; TKI, Tyrosine Kinase Inhibitor; ALK, anaplastic lymphoma kinase; POS-1, ROS proto-oncogene 1; ICIs, immune checkpoint inhibitors; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; PD-L2, programmed cell death ligand-2; RT, radiotherapy; AEs, adverse events;

Declarations

Disclosure

No authors report any conflict of interest.

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Tables

Table 1. Characteristics of the studies included in the meta-analysis												
Study, year (reference)	country	treatment	Study type	Whether randomized	Treat line	No. Of patients	ORR (%)	DCR (%)	PFSR6m(%)	OSR1y (%)	HR for PFS	P f C
James W Welsh, 2019 ^[43]	USA	ICIs+RT Vs ICIs	Phase 1/2	Random	First- line	16 36	37 22	81	87	86	NA	NA
Angel Qin 2019 ^[44]	USA	ICIs+RT	Pilot	Non- random	At least Second	12	25	50	33	42	NA	NA
Paul Lesueur 2018 ^[45]	France	ICIs+RT	Retrospectively	Non- random	not requied	104	NA	NA	17.9	47.0	NA	NA
Francesco Fiorica 2018 ^[46]	Italy	ICIs+RT Vs ICIs	Retrospectively	Non- random	At least Second	15 20	NA	NA	60 33	57.8 27.4	0.60 [0.39- 0.94]	C [C
Corey C. Foster 2019 ^[47]	USA	ICIs+RT	Retrospectively			228	NA	NA	NA	65		
V. Moreno 2017 ^[48-50]	Spain	ICIs+RT Vs ICIs	Phase 1	Non- random	First- line	33 20	18.2 40	72.7 60	NA	NA	NA	C [C 1
Willemijn S. M. E. Theelen 2019 ^[51]	Nether- Lands	ICIs+RT Vs ICIs	Phase 2	Random	At least Second	36 40	47.2 22.5	72.2 47.5	53.11 35.6	54.83 36.09		NA
James Welsh 2017 ^[52]	USA	ICIs+RT	Phase 1	Random		17	24	71	53	47	0.71 [0.42- 1.18]	C [C 1
Abraham Chachoua 2019[NCT02221739]	USA	ICIs+RT	Phase 2	Non- random	At least Second	39	17.9	NA	NA	NA	NA	NA
Jyoti D. Patel 2020[NCT03223155]	USA	ICIs+RT	Phase 1	Non- random	At least Second	35	68	74	NA	NA	NA	NA
				Non- random	At least Second						NA	NA
				Non- random	First- line							NA

Table2 The combined results of subgroup				
Analyses	Pooled ORR, model, Number of studies	Pooled DCR, model, Number of studies	Pooled PFSR6m, model, Number of studies	Pooled OSR1y, model, Number of studies
Anti-PD-1/PD-L1 antibody +RT	31.5% [16.4%-46.6%] Random, 4	72.1% [63.3%-80.9%] Fixed, 4	50.0% [20.6%-79.5%] Random, 5	59.7% [48.1%-71.2%] Random, 6
Anti-CTLA4 antibody+RT	19.5% (9.1%-29.8%) Fixed, 2	NA	NA	NA
Prospective, ICIs+RT	33.9% [18.6%-49.3%] Random, 7	72.4% [65.3%-79.5%] Fixed, 6	56.9% [33.9%-79.9%] Random, 4	58.9% [38.5%-79.4%] Random, 4
concurrent therapy	21.3% [13.9%-28.6%] Fixed, 5	71.8% [62.0%-81.6%] Fixed, 4	58.9% [26.2%-91.7%] Random, 3	59.7% [29.7%-89.8%] Random, 3
sequential therapy	NA	NA	55.2% [41.6%-68.8%] Fixed, 2	55.7% [42.1%-69.3%] Fixed, 2
Low dose RT	30.2% [10.7%-49.6%] Random, 3	69.7% [59.8%-79.6%] Fixed, 3	45.9% [27.0%-64.8%] Random, 2	51.6% [37.5%-65.6%] Fixed, 2
High dose RT	22.3% [12.8%-31.8%] Fixed, 3	76.6% [62.2%-90.9%] Fixed, 2	71.1% [37.9%-104.4%] Random, 2	67.4% [29.2%-105.6%] Random, 2
First-line group	53.8% [23.6%-84.1%] Random, 2	6.5% [65.0%-88.1%] Fixed, 2	NA	NA
At least second-line	25.9% [14.7%-37.2%] Random, 5	69.9% [60.9%-78.9%] Fixed, 4	51.1% [40.3%-61.9%] Fixed, 4	51.8% [40.9%-62.7%] Fixed, 4
Abbreviations: ORR, objective response rate; DCR, disease control rate; PFSR6m, six-month progression-free survival rates; OSR1y, one-year overall survival rate; ICIs, immune checkpoint inhibitors; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; RT, radiotherapy;				

Figures

Figure 1

Flowchart of the study selection procedure

Figure 2

Forest plot of the combined ORR, DCR, PFSR6m, or OSR1y of ICLs combined with radiotherapy as treatment for advanced lung cancer. Among the ten studies, seven studies assessed the ORR of ICLs combined with radiotherapy(a). The pooled DCR for the six studies is shown in (b). Six studies provided the PFSR6m and seven provided the OSR1y, which are shown in (c) and (d).

Figure 3

Forest plot of the combined HR values of PFS and OS of two-armed studies. Among the ten studies, two studies assessed the HR values of PFS(a). The combined HR values of OS for the three studies is shown in (b).