The efficacy and safety of immunotherapy and palliative radiotherapy in metastatic non-small cell lung cancer patients: a systematic review and meta-analysis

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Research Article

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Abstract

Objective:

Palliative radiotherapy (pRT) is usually used in the treatment of metastatic non-small cell lung cancer (mNSCLC). However, whether pRT could influence the outcomes of mNSCLC patients who considered immune checkpoint inhibitors (ICIs) as maintenance treatment is still under debate. Here we did a systematic review and meta-analysis to assess the efficacy and safety of this combination strategy in mNSCLC patients.

Methods:

The PubMed, Cochrane and Embase databases were searched for prospective studies and randomized controlled trials (RCTs). The main outcomes were overall survival (OS), progression-free survival (PFS), disease control rate (DCR), objective response rate (ORR), and treatment-related adverse events. All data was analyzed with Stata v 16.0 and Review Manager version 5.4 software.

Results:

A total of 12 studies were included. pRT plus ICIs was significantly associated with improved DCR (OR=2.27, 95%CI [1.27, 4.04]; p=0.008), OS (HR=0.66, CI [0.54, 0.80]; p<0.0001) and PFS (HR=0.60, CI [0.44, 0.81]; p=0.0009). In safety analyses of III-IV grade adverse events (AEs), patients receiving ICIs plus pRT showed no statistically significant difference (p=0.43) when compared with those in the control group.

Conclusion:

Patients with mNSCLC may benefit from the ICI and pRT combination therapy with acceptable incidence of grade III-IV AEs.

Introduction

Currently, non-small cell lung cancer (NSCLC), which accounts for 80–85% of all lung cancer cases, continues to be the leading cause of cancer mortality worldwide[1]. Five-year overall survival rates range from 14–49% for node-negative NSCLC, and < 5% for locally advanced, unresectable NSCLC[2]. Improving the prognosis of metastatic NSCLC (mNSCLC) is currently one of the major challenges in thoracic oncology. Immunotherapy provides more treatment options for mNSCLC patients.

With the rapid development of immunotherapy, immune checkpoint inhibitors (ICIs) targeting programmed death 1 (PD-1) and its ligand (PD-L1) and others have shown excellent clinical efficacy and have revolutionized the treatment landscape of several solid tumors, especially in mNSCLC. At present, PD-1/PD-L1 inhibitors, including pembrolizumab and atezolizumab, has gradually moved from the second-line to the first-line setting in mNSCLC patients with high PD-L1 expression (≥ 50%)[3, 4]. Despite impressive achievements, the disturbing limitation of ICIs has been revealed that only a small proportion of patients will benefit from its application[5]. In addition, acquired resistance with unclear mechanisms may ultimately develop. In order to extend the clinical benefits of ICIs for more patients, and to overcome possible resistance, several explorations have been performed, and the combination strategy becoming the most promising one.

Radiotherapy is an important treatment strategy for lung cancer which could eliminate the cancer cells by high energy radiation[6]. Radiotherapy can be applied in all stages of lung cancer and is also one of the important methods to prevent and treat distant metastasis of lung cancer[7]. Improvements have been made in the outcomes of patients with NSCLC due to advancements in radiotherapy (RT) techniques, the use of concurrent chemotherapy with RT, and the emergence of immunotherapy as first- and second-line treatment in the metastatic setting. In addition, the National Comprehensive Cancer Network (NCCN) guidelines recommend that isolated or limited metastatic sites (oligometastases) could use definitive local therapy (RT or SBRT) which should be individualized based on goals of care, symptoms, performance status, and logistical considerations[8].

Evidence has revealed that radiation can exert potent immunomodulatory effects, exposing the tumor immunogenicity and providing an antitumor microenvironment[9].

The abscopal effect, a phenomenon that had previously been reported in patients treated with radiotherapy, is becoming more arresting, especially with the rise of immunotherapy. Currently, there is a growing consensus that the combination of radiotherapy and immunotherapy could increase the occurring rates of abscopal effect[10]. With a result, the synergistic effect improves the response rate of metastatic NSCLC patients and prolong their survival period. Stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), can be safely and effectively delivered to patients with inoperable early-stage and oligometastatic NSCLC, including those with poor pulmonary function at baseline[11]. It can deliver high doses to relatively small target lesions, thus achieving more than 90% local control and substantially improving prognosis with a low risk of toxicity[12]. It is important to note that SBRT has been shown to have significant advantages over conventional radiation therapy, potentially due to its stronger immune activation[13].

Therefore, combining ICIs and radiotherapy at the right time becomes the main topics of the current researches. However, a great controversy exists when combining the ICIs and radiation, especially for stage IV NSCLC patients. In this systematic review and meta-analysis, we assessed the efficacy and safety of ICIs combined with pRT for mNSCLC patients, trying to explore the impact of applying pRT on the prognosis of these patients in the setting of immunotherapy.

Methods

2.1. Registration
This study was registered in PROSPERO (https://www.crd.york.ac.uk/prospero/) and the reference number is CRD42021289352. This study was performed based on the PRISMA checklist.

### 2.2 Search strategy

We identified articles published in the English language by searching PubMed, Embase and the Cochrane Library from inception to October 20th, 2021. The full text of eligible studies was obtained from PubMed, and Embase. The relevant references from related reviews were also examined. The major search terms were (“immune checkpoint inhibitor” or “immune checkpoint blockade” or “PD-1 antibody” or “PD-L1 antibody” or “CTLA-4 inhibitor” or “nivolumab” or “pembrolizumab” or “iplimumab” or “atezolizumab” or “durvalumab”) and (“cancer” or “non-small cell lung cancer” or “carcinoma” or “pulmonary adenocarcinoma” or “stage IV NSCLC” or “metastatic NSCLC”) and (“OS” or “overall survival” or “survival” or “PFS” or “progression-free survival” or “efficacy” or “ORR” or “response” or “overall response”) and (“radiation” or “radiotherapy” or “conventional radiation therapy” or “CRT” or “Stereotactic body radiation therapy” or “SBRT” or “stereotactic ablative radiotherapy” or “SABR”) and (“prospective study” or “randomized controlled trial” or “clinical trial”). Two authors independently screened the titles and abstracts of retrieved articles. The search strategy is provided in [Supplemental Table 1](#) (the searching strategy).

### 2.3 Inclusion and exclusion criteria

This systematic review and meta-analysis included studies that met the following inclusion criteria: (I) NSCLC confirmed histologically; (II) NSCLC patients with one or more metastatic lesions; (III) PD-1 /PD-L1 / CTLA4 inhibitors as first or subsequent line therapy with or without radiotherapy (conventional radiation therapy (RT), or SBRT); (IV) outcome of interests (i.e. OS, PFS) were reported from the original prospective or randomized controlled trial (RCT) studies. Articles were excluded based on the following criteria: (I) patients were not metastatic NSCLC; (II) repeated reports from the same institute or population; (III) the outcomes of interest [median OS or PFS and/or hazard ratios (HRs)] of mNSCLC patients could not be extracted from publication or survival curves; and (IV) animal studies, reviews, or comments. The full-text article of any study that appeared to meet the inclusion criteria was retrieved for further examination. Disagreements between reviewers regarding data abstraction were resolved through discussion.

### 2.4. Data extraction and quality assessment

Data were extracted and recorded in a predefined information sheet by two authors independently. Study characteristics (first author, year of publication, number of patients, treatment strategy, details of immune checkpoint inhibitors, RT regimens) and outcome (median OS and PFS) data were extracted from the included articles. All discrepancies were discussed to reach consensus. The assessment of the risk of bias in included studies was conducted independently by two authors using the methodological index for non-randomized studies (minors) checklist[14]. ([supplemental table 2](#) Quality assessment of included studies)

### 2.5. Statistical analysis

We defined the median OS as the primary outcome. For each study, the hazard ratio (HR) with corresponding 95% confidence intervals (CI) was directly extracted from the research article or estimated using Kaplan-Meier survival curves[15]. Median OS and PFS were pooled using weight calculated from the 95% confidence interval (95% CI) and sample size.

We conducted a meta-analysis based on the survival outcome data and adverse reactions reported in the articles. Hazard ratios for OS and PFS, comparing the use of pRT + ICIs vs. ICIs in mNSCLC, were aggregated in a formal meta-analysis using a fixed or random effect model. The heterogeneity was assessed using $I^2$ statistics with $P$ values $< 0.05$ or $I^2$ values $> 50\%$, considering to be significant. An appropriate statistical model (fixed or random-effects model) was used to pool the percentages and corresponding 95% confidence intervals (CIs) based on the results of the heterogeneity test. For all these analyses, $P$ values of $< 0.05$ indicated statistical significance. Publication bias was checked with Begg’s and Egger’s test for primary endpoints. All analyses were performed with Stata v 16.0 and Review Manager version 5.4 software.

### Result

#### Search results.

After screening the titles and abstracts, 728 records were obtained. 181 duplicate studies were excluded. 489 articles comparing irrelevant papers, reviews case reports were excluded based on the titles and abstracts. And a total of 46 papers were excluded as they were retrospective studies, or studies in other cancer types or conference abstracts with limited data. Finally, twelve publications were eventually identified for the final meta-analysis. The PRISMA checklist of this study is shown in [Supplemental Table 3](#) (the PRISMA checklist of included studies). The electronic database search process is illustrated in [Figure 1](#).

### Characteristics of Included Studies.

A total of 915 patients were enrolled in the 12 studies for this research. Among these included studies[16-27], four of them[24-27] were randomized controlled trials and other eight articles were prospective studies. All studies included at least one arm treated with combination therapy using ICIs and pRT. Five studies compared the administration of SBRT plus ICIs with PD-1/PD-L1 inhibitors alone. And the other five articles were single-arm studies using pRT and ICIs to treat
mNSCLC. Of the 12 studies, eight reported the specific radiation dose and fraction pattern and two didn’t describe these details. All the studies included mNSCLC patients and ten of them set the concurrent radiation therapy with ICIs.

The baseline characteristics of the included studies are presented in Table 1.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study type</th>
<th>Region</th>
<th>Cancer detail</th>
<th>Treatment strategy</th>
<th>radiotherapy details</th>
<th>Timing of RT</th>
<th>Total sample</th>
<th>Sample RT/SBRT+ICIs</th>
<th>Sample ICIs</th>
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<tr>
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<td>prospective</td>
<td>America</td>
<td>stage IV/NSCLC</td>
<td>RT + ICIs</td>
<td>30Gy/10f; 20Gy/5f</td>
<td>sequence</td>
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<td>213</td>
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<tr>
<td>Narek</td>
<td>2017</td>
<td>prospective</td>
<td>America</td>
<td>metastatic</td>
<td>RT + ICIs</td>
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<td>Multiple</td>
<td>pretreated advanced NSCLC</td>
<td>SBRT + ICIs vs. ICIs</td>
<td>9Gy/3f</td>
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<td>53</td>
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<td>20</td>
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<td>12</td>
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<td>76</td>
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<tr>
<td>Willeijn</td>
<td>2021</td>
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<td>Multiple</td>
<td>metastatic NSCLC</td>
<td>RT/SBRT+ICIs vs. ICIs</td>
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<td>concurrent</td>
<td>148</td>
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</table>

abbreviations: RCT: randomized controlled trials; RT: radiotherapy; SBRT: stereotactic body radiation therapy; ICIs: immune checkpoint inhibitors; NSCLC: non-small cell lung cancer; ORR: objective response rate; DCR: disease control rate; OS: overall survival; PFS: progression-free survival.

Results of meta-analysis.

Objective Response Rate

We extracted the ORR of the experimental cohort and controlled cohort in three studies. Due to the high heterogeneity (I² =86%) among the studies, the random effect model was used to evaluate the overall odds ratio (OR). As illustrated by Figure 2A, the effect of pRT combined with ICIs on ORR was similar with that of the ICIs group (OR=0.68, 95%CI [0.12, 3.74], p=0.65). This result indicated that pRT plus ICIs had no significant influence on the response rate in stage IV NSCLC. In the single arm group of pRT and ICIs, the overall ORR was 0.33 (CI: [0.18, 0.48]) with significant heterogeneity (I²=91%) (Figure 2B).

Disease Control Rate.

RR for the DCR was available from two trials. The pooled analysis of DCR using the fixed effect model is shown in Figure 3A. There was no statistical heterogeneity between the studies (I²=0%). The result showed that pRT combined with ICIs significantly increased the DCR (OR=2.27, 95%CI [1.27, 4.04];
Immune memory in long-term CD8+T cell survivors from fractionated radiotherapy could not produce durable anti-tumor immunity, whereas combination of RT and ICIs could induce memory-enhanced protective immunity. RT induces and enhances the immunogenicity of tumors by increasing the expression of tumor-associated antigens, the major histocompatibility complex, and damage-associated molecular patterns. RT-induced necrosis factor α (TNF-α) and PD-1/PD-L1 inhibitor could reduce radiation-induced local accumulation of MDSCs by the TNF-α axis. Moreover, single hypo fractionated radiotherapy could not produce durable anti-tumor immunity, whereas combination of RT and ICIs could induce memory-enhanced protective immune memory in long-term CD8+T cell survivors. Radiation may rescue response in patients who have acquired resistance to checkpoint inhibition. The improved survival benefit and better disease control rates associated with combined radio-immunotherapy regimen could be results of the following mechanisms: (i) Typically, the immunogenic cell surface was down-regulated in NSCLC, which is an important cause of immune resistance and immune escape. RT induces and enhances the immunogenicity of tumors by increasing the expression of tumor-associated antigens, the major histocompatibility complex, and damage-associated molecular patterns. (ii) Recovery of CD8+T cells after PD-1 / PD-L1 inhibitor treatment induced production of tumor necrosis factor α (TNF-α) and PD-1/PD-L1 inhibitor could reduce radiation-induced local accumulation of MDSCs by the TNF-α axis. Moreover, single hypo fractionated radiotherapy could not produce durable anti-tumor immunity, whereas combination of RT and ICIs could induce memory-enhanced protective immune memory in long-term CD8+T cell survivors. (iii) Radiation may rescue response in patients who have acquired resistance to checkpoint inhibition.

Overall Survival and Progression-Free Survival.

To evaluate the role of radiation therapy on OS and PFS in metastatic NSCLC patients treated with ICIs, a meta-analysis of PFS and OS between pRT with ICIs versus ICIs in stage IV NSCLC was performed. The fixed effect model was utilized as low risks of heterogeneity were found in these analyses. The relative benefit in improving OS and PFS after receiving pRT and ICIs was significant (OS: HR=0.66, CI [0.54, 0.80] P=0.0001; PFS: HR=0.60, CI [0.44, 0.81] P=0.0009, respectively) (figure 4A, B). When it comes to the single arm settings, the overall OS was 11.67 months (CI [6.87, 16.46]), and the overall PFS was 4.93 months (CI [2.83, 7.04]) (figure 4C, D).

Subgroup analysis.

Individual subgroup analyses were performed based on the fractionation of RT. In consideration of the characteristics of the extracted data, we defined the “three fractions” as the standard group. The result showed that the overall DCR for these metastatic NSCLC patients was 0.53 (CI: [0.33; 0.73]) while using SBRT (random effects model, \( P = 0.82 \)). For the standard group, the DCR could be 0.58 (CI: [0.28; 0.87]) (using random effects model, \( P = 0.90 \)) (supplement figure 1). The meta-analysis of the overall DCR of metastatic NSCLC patients when the radiation type is SBRT (A) Subgroup analysis of fractionation of SBRT was performed (B). With regards to ORR, the overall ORR was 0.26 (CI: [0.15; 0.38]) (random effects model, \( P = 0.56 \)) when the SBRT was applied as palliative radiotherapy. And while the fractionation is more than or equal to three times, the ORR was 0.27 (CI: [0.12; 0.41]) (supplement figure 2). The meta-analysis of the overall ORR of metastatic NSCLC patients when the radiation type is SBRT (A). Subgroup analysis of fractionation of SBRT was performed (B) for patients who were treated with more fractions of SBRT.

Safety.

We also explored the safety profile of the combined group and single treatment group. Due to the great homogeneity, we used the fixed effect model to assess the overall effect. And the results showed that the incidences of III-IV grade adverse events (AEs) (AEs were defined using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0) were similar between the two groups (\( p = 0.43 \)) (figure 5).

Assessment of publication bias.

The funnel plots of the included studies were conducted using DCR, ORR, OS and PFS data. The funnel plots were well symmetrized (Supplemental Figure 3). The funnel plots of the included studies, suggesting that the results were less likely to be affected by publication bias. And the sensitivity analysis of DCR and ORR showed that the outcome of meta-analysis was stable and reliable (supplemental figure 4). The sensitivity analysis of DCR and ORR.

Discussion

Although PD-1/PD-L1 inhibitors are used as first or second-line therapy for advanced NSCLC patients, it is still controversial whether the application of local palliative radiotherapy will affect survival outcomes of mNSCLC patients. In this systematic review and meta-analysis, we included 12 prospective studies and evaluated the benefit and the outcome of patients with metastatic NSCLC when treated with ICIs with or without palliative RT to the primary tumor. Our results suggested that combination therapy using PD-1/PD-L1 inhibitors and RT may improve OS, PFS, and DCR in patients with mNSCLC. This suggests that combining immunotherapy with other therapies, such as radiation, could ultimately lead to improved survival outcomes. When considering the side effects of combing immunotherapy and pRT, the incidence of III-IV grade AEs upon combined treatment was not statistically increased when compared to the single treatment strategy (\( p = 0.43 \)). Overall, AEs are generally tolerable. In addition, in the subgroup analysis, we found that the DCR and ORR showed that the outcome of meta-analysis was stable and reliable (supplemental figure 4). The sensitivity analysis of DCR and ORR.

Recently, a meta-analysis assessed the efficacy and safety of RT and ICIs in advanced NSCLC patients with brain metastases (BMS)\(^{22}\). The results included 19 cohort studies and more than 15,000 patients, showing a 23% reduction in the risk of death and roughly equal risk of grade 3-4 AEs. This conclusion is consistent with the analysis of this study, though the patients were not limited to BMS. Another meta-analysis included 20 studies, including 9 non-randomized controlled trials (NRCT) and 9 single-ARM studies, totaling 2027 patients with advanced NSCLC (Stage III-IV)\(^{29}\). The conclusion is also consistent with our findings that the combination of ICIs and pRT can improve OS, PFS and DCR in patients with advanced NSCLC.

The improved survival benefit and better disease control rates associated with combined radio-immunotherapy regimen could be results of the following mechanisms: (i) Typically, the immunogenic cell surface was down-regulated in NSCLC, which is an important cause of immune resistance and immune escape. RT induces and enhances the immunogenicity of tumors by increasing the expression of tumor-associated antigens, the major histocompatibility complex, and damage-associated molecular patterns\(^{30}\). (ii) Recovery of CD8+T cells after PD-1 / PD-L1 inhibitor treatment induced production of tumor necrosis factor α (TNF-α) and PD-1/PD-L1 inhibitor could reduce radiation-induced local accumulation of MDSCs by the TNF-α axis. Moreover, single hypo fractionated radiotherapy could not produce durable anti-tumor immunity, whereas combination of RT and ICIs could induce memory-enhanced protective immune memory in long-term CD8+T cell survivors\(^{32}\). (iii) Radiation may rescue response in patients who have acquired resistance to checkpoint inhibition.
inhibitors[33]. (iv) RT also regulates the tumor microenvironment. Inflammatory signaling occurs after radiation therapy by activating cell survival pathways and stimulating the innate immune system[32, 34]. Both direct and indirect radiation effects trigger inflammatory cytokine signaling (IL-1 TNF-α) and immune cell recruitment[35].

However, this meta-analysis has some limitations. First, not all of the included studies are RCT studies. This may be because many related studies are ongoing. Second, the sequence of administration of palliative RT varies between the included studies. And due to the limitation of the selected studies, we could not evaluate the impact of optimal sequence of RT when RT and ICIs were combined in stage IV NSCLC. Third, several literatures have mentioned the relationship between the expression level of PD-1/PD-L1 and survival outcomes. And this analysis was not performed because of the limited data. Fourth, although we only included prospective and RCT studies, the heterogeneity of the included studies was inevitably existed, such as the differences of the baseline characteristics of the included patients, and the treatment details of the individuals. Therefore, we will update this meta-analysis when more prospective studies are reported.

**Conclusion**

Using ICIs and pRT as the treatment strategy for stage IV NSCLC patients may improve their OS, PFS and DCR with acceptable toxicity. Further large-scale RCTs are needed to confirm these results.

**Declarations**

**Ethics approval and informed consent**

Not applicable.

**Consent for publication**

Not applicable.

**Author's contributions**

Dedong Cao, Wei Ge, Dingjie Zhou, and Nan Zhao participant in the study conception, design, and Dedong Cao contributed to the final approval of the submitted version. Yongfa Zheng and Pingpo Ming finished the collection and interpretation of data. Dedong Cao, Ximing Xu, Dingjie Zhou and Huilin Xu contributed to the completion of table and figures. Wei Ge, Dingjie Zhou, Nan Zhao and Dedong Cao contributed to the writing of the manuscript. All the authors have read and approved the final manuscript.

**Declaration of competing interest**

The authors declare that they have no competing interests.

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**Data Availability**

All data generated or analyzed during this study are included in this published article and its supplementary information files.

**References**


Figures
Figure 1

Literature screening process

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<tr>
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<tr>
<td>Willemijn 2021</td>
<td>30</td>
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</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>146</strong></td>
<td><strong>156</strong></td>
<td><strong>100.0%</strong></td>
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<tr>
<td><strong>Total events</strong></td>
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Heterogeneity: Tau² = 1.96; Chi² = 14.78, df = 2 (P = 0.0006); I² = 86%
Test for overall effect: Z = 0.45 (P = 0.65)

Figure 2

A: The meta-analysis of ORR in metastatic NSCLC patients treated with radiotherapy and immune checkpoint inhibitors versus immune checkpoint inhibitors alone. B: The overall effect of ORR was synthesized based on single arm studies.
Figure 3

A: The meta-analysis of DCR in metastatic NSCLC patients treated with radiotherapy and immune checkpoint inhibitors versus immune checkpoint inhibitors alone. B: The overall effect of DCR were synthesized based on single arm studies.

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<thead>
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<td>Willemijn 2021</td>
<td>47</td>
<td>72</td>
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</tbody>
</table>

Total (95% CI) 105 96 100%

Heterogeneity: $I^2 = 0.00$, $I^2 = 0.34$, df = 1 ($P = 0.56$); $I^2 = 0$

Test for overall effect: $Z = 2.84$ ($P = 0.005$)

---

Figure 4

A: Hazard Ratio

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
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<th>Weight</th>
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<tr>
<td>Willemijn 2021</td>
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<td>0.2011</td>
<td>58.8%</td>
<td>0.67 [0.45, 0.99]</td>
</tr>
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</table>

Total (95% CI) 100% 0.60 [0.44, 0.81]

Heterogeneity: $I^2 = 0.71$, df = 1 ($P = 0.40$); $I^2 = 0$

Test for overall effect: $Z = 3.33$ ($P = 0.0009$)

---

B: Hazard Ratio

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narek 2017</td>
<td>-0.5471</td>
<td>0.2421</td>
<td>17.8%</td>
<td>0.58 [0.36, 0.93]</td>
</tr>
<tr>
<td>Willemijn 2021</td>
<td>-0.3953</td>
<td>0.1137</td>
<td>82.2%</td>
<td>0.67 [0.54, 0.84]</td>
</tr>
</tbody>
</table>

Total (95% CI) 100% 0.66 [0.54, 0.80]

Heterogeneity: $I^2 = 0.32$, df = 1 ($P = 0.57$); $I^2 = 0$

Test for overall effect: $Z = 4.13$ ($P = 0.0001$)

---

C: Effect Size

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect Size with 95% CI</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silvia 2018</td>
<td>7.60 [3.30, 11.80]</td>
<td>23.75</td>
</tr>
<tr>
<td>Mattes 2021</td>
<td>15.65 [6.05, 25.20]</td>
<td>9.92</td>
</tr>
<tr>
<td>Willemijn 2021</td>
<td>19.20 [14.60, 23.80]</td>
<td>22.73</td>
</tr>
<tr>
<td>Overall</td>
<td>11.67 [6.87, 16.48]</td>
<td>19.68</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 29.84$, $I^2 = 84.20$,

Test of $b = 0$ (Q): $p = 0.00$

Test of $b = 0$ (Z): $z = 4.77$, $p = 0.00$

---

D: Effect Size

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect Size with 95% CI</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narek 2017</td>
<td>4.45 [1.15, 7.85]</td>
<td>15.29</td>
</tr>
<tr>
<td>Silvia 2018</td>
<td>2.61 [0.93, 5.29]</td>
<td>22.26</td>
</tr>
<tr>
<td>Silvia 2018</td>
<td>2.70 [1.45, 3.96]</td>
<td>22.17</td>
</tr>
<tr>
<td>Qin A. 2020</td>
<td>2.35 [0.83, 3.89]</td>
<td>4.80</td>
</tr>
<tr>
<td>Mattes 2021</td>
<td>6.66 [3.95, 10.40]</td>
<td>7.18</td>
</tr>
<tr>
<td>Willemijn 2021</td>
<td>9.60 [4.83, 11.90]</td>
<td>19.05</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 4.52$, $I^2 = 4.52$,

Test of $b = 0$ (Q): $p = 0.00$

Test of $b = 0$ (Z): $z = 4.05$, $p = 0.00$

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>RT+ICls Events</th>
<th>ICls Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H. Fixed, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moreno 2018</td>
<td>8</td>
<td>33</td>
<td>2</td>
<td>20</td>
<td>14.8% 2.42 [0.57, 10.30] 2018</td>
</tr>
<tr>
<td>Bozorgmehr 2020</td>
<td>7</td>
<td>41</td>
<td>9</td>
<td>60</td>
<td>43.5% 1.14 [0.46, 2.81] 2020</td>
</tr>
<tr>
<td>Welsh 2020</td>
<td>7</td>
<td>40</td>
<td>7</td>
<td>40</td>
<td>41.7% 1.00 [0.39, 2.59] 2020</td>
</tr>
</tbody>
</table>

Total (95% CI) 114 120 100.0% 1.27 [0.70, 2.30]

Total events 22 18

Heterogeneity: $\chi^2 = 1.07$, df = 2 (P = 0.59); $I^2 = 0\%$

Test for overall effect: Z = 0.80 (P = 0.43)

Figure 5

The meta-analysis of the incidence of III-IV grade adverse events (AEs)

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- supplementfigure1.pdf
- supplementfigure2.pdf
- supplementfigure3.pdf
- supplementfigure4.pdf
- supplementtable1.pdf
- supplementtable2.pdf
- supplementtable3.pdf