INPLASY PROTOCOL

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Corresponding author:
Zexi Xu

1161429869@qq.com

Author Affiliation:
Renmin Hospital of Wuhan University

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The authors declare no conflict of interest.

Combination of radiotherapy and Immune checkpoint inhibitors for advanced Non-small cell lung cancer: A systematic review and meta-analysis

Xu, Z[1]; Zhang, H[2]; Weng, Y[3]; Jin, Y[4]; Peng, M[5].

Review question / Objective: **The aim of this meta-analysis of randomized controlled trials is to evaluate the efficacy and safety of Immune checkpoint inhibitors combined with radiotherapy for advanced non-small cell lung cancer.**
Condition being studied: **Lung cancer is one of the malignant tumors with the highest incidence worldwide, and the death rates are about 90% of the diagnosis rates.There are four major histological types of lung cancer, there are: small-cell lung cancer(SCLS), squamous cell cancer(SCC), adenocarcinoma, large-cell cancer.Owing to the clinical management of the last three types is similar, they are classified in non-small-cell lung cancers. Unfortunately, only few people whose cancer can be removed by an operation, thus radiotherapy is used when surgery is unsuitable, but usually radiation therapy is not used alone.In recently, immunotherapy have showed good efficacy in the treatment of lung cancer, however only a minority of patients derived a durable benefit. There is some hope that combination of radiotherapy with immunotherapy to improve the survival of patients.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 June 2020 and was last updated on 03 June 2020 (registration number INPLASY202060011).

INTRODUCTION

Review question / Objective: **The aim of this meta-analysis of randomized controlled trials is to evaluate the efficacy and safety of Immune checkpoint inhibitors combined with radiotherapy for advanced non-small cell lung cancer.**

Rationale: **Radiation therapy is one of the traditional therapies for non-small cell lung cancer, some preclinical studies have show that radiotherapy can improve the response of lung cancer to immunotherapy, owing to the increased tumor antigen release and improved antigen presentation**

in irradiated tumors. So, there are potential synergistic effect between immunotherapy and radiotherapy.

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METHODS

Search strategy: We will search, with no time restrictions, the following databases for relevant English language literature: PubMed (MEDLINE), Embase,the Cochrane Central Register of Controlled Trials (CENTRAL) , US-clinical trials and China National Knowledge Infrastructure Database (CNKI).The fllowing keywords were used:"Carcinoma,Non-Small-Cell Lung", "Nonsmall Cell Lung Cancer", "Immunotherapy", "Programmed Cell Death 1 Receptor", "Programmed Cell Death 1 Ligand 1", "CTLA-4 Antigen", "Durvalumab", "Pembrolizumab", "Atezolizumab", "Nivolumab", "Tremelimumab" , "Ipilimumab","Radiotherapy","randomized controlled trial".The electronic database search will be supplemented by a manual search of the reference lists of included articles.

Participant or population: The included participants will be adults who were diagnosed with histopatholoical and cytological criteria and without the restriction of clinical stages or pathological classification.The gender, ethnicity, education and economic status of the patients are not limited.

Intervention: The intervention in the experimental group was immunotherapy combined with radiotherapy or chemoradiotherapy.

Comparator: Immunotherapy monotherapy was the comparation.

Study designs to be included: Randomized clinical trials will be included irrespective of blinding, publication status or language.

Eligibility criteria: (1)Randomized clinical trials (RCTs) of non-small cell lung cancer; (2)reporting outcome and/or toxicity for Non-Small-Cell Lung cancer patients treated with PD-1/PD-L1/CTLA-4 Inhibitors combined with/without radiotherapy.

Information sources: We searched for articles in PubMed, EMBASE, Cochrane Library, US-clinical trials and China National Knowledge from their inception date to June 2020. We also expanded our search by reviewing abstracts and presentations from major conferences, including the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) meeting, in order to make sure that all eligible articles could be screened. Finally, references to the studies included in the final selection were also checked.

Main outcome(s): Overall survival and progression-free survival of patients.

Additional outcome(s): Disease control rate (DCR) ,objective response rate(ORR),toxic effects will be defined as the secondary outcomes.

Data management: The following records were collected from the eligible studies: the name of first author, publication year, phase of RCT, histological type of lung cancer, numbers of patients (with and

without PORT),line of therapy, treatment regimen of study arm, Overall survival, Progression-free survival, disease control rate (DCR) ,objective response rate(ORR), locoregional recurrence and distant hematogenous metastases data, and occurrence of grade 3–4 adverse events of cancer patients in each arm. Two investigators extracted data from the articles independently, and controversies were resolved via discussion or determined by the third reviewer.

Quality assessment / Risk of bias analysis: The evaluation of study quality was carried out by the "Risk of bias" tool in Review Manager (RevMan 5.3; The Cochrane Collaboration, Oxford, United Kingdom). The methodological quality of RCTs was assessed by Cochrane risk of bias tool, which consists of the following five domains: sequence generation, allocation concealment, blinding, incomplete data, and selective reporting. An RCT was finally rated as "low risk of bias" (all key domains indicated as low risk), "high risk of bias" (one or more key domains indicated as high risk), and "unclear risk of bias".Two investigators evaluated the risk of bias independently. All discrepancies were settled by consulting the third reviewer.

Strategy of data synthesis: Statistical analysis was performed using the software Review Manager 5.3 (Cochrane Collaboration, Oxford,UK) and STATA MP14.0 (Stata Corporation, College station, TX, USA). Because the median survival or survival rates at a specific point in time were not expected to be reliable surrogate measures for the pooled survival analysis, hazard ratios (HRs) and their 95% CI were used as summary statistics for OS in the present meta analysis. Crude HR with 95% CI were either extracted directly from the original reports or calculated by the Kaplan- Meier curves . I2 was used to assess heterogeneity across studies , with I2 values of 0%, 25%, 50% and 75% representing no, low, moderate and high heterogeneity, respectively.According to the Cochrane review guidelines, if severe heterogeneity was present at I2 >50%, the random effect models were chosen, otherwise the fixed effect models were used. In addition, we conducted subgroup and meta regression analysis to search for the source of heterogeneity, sensitivity analysis was conducted by deleting each study individually to evaluate the quality and consistency of the results. Publication bias was assessed by both Egger's test and Begg's test.If evidence of publication bias was observed, the trim and fill method was applied to correct the bias. A P value <0.05 was considered to be statistically significant.

Subgroup analysis: If the necessary data are available, subgroup analyses will be carried out for people with different types of pathological type.In addition, the sequencing of radiation therapy and immunotherapy seems important, so we will analysis the differences effect on outcome of radiotherapy given before or concurrently or after to immunotherapy.

Sensibility analysis: Sensitivity analysis was conducted by deleting each study individually to evaluate the quality and consistency of the results,We use STATA 16 software to conduct it.

Language: English.

Country(ies) involved: China.

Keywords: Meta-analysis; Radiotherapy; Immune checkpoint inhibitors; Survival.

Contributions of each author:
Author 1 - Zexi Xu.
Author 2 - Huibo Zhang.
Author 3 - Yiming Weng.
Author 4 - Yao Jin.
Author 5 - Min Peng.