May 01, 2024 Version 2

kpoint Inhibitors Combined with Radiotherapy or Chemoradiotherapy for Advanced Non-Small Cell Lung Cancer: A Systematic Review and Single-Arm Meta-Analysis V.2

DOI
dx.doi.org/10.17504/protocols.io.261ge54njg47/v2

ran cui[1], ran cui[1]

[1]The First People's Hospital of Neijiang

r ran cui
The First People's Hospital of Neijiang

OPEN ACCESS

DOI: dx.doi.org/10.17504/protocols.io.261ge54njg47/v2

Protocol Citation: ran cui, ran cui 2024. kpoint Inhibitors Combined with Radiotherapy or Chemoradiotherapy for Advanced Non-Small Cell Lung Cancer: A Systematic Review and Single-Arm Meta-Analysis. **protocols.io** **https://dx.doi.org/10.17504/protocols.io.261ge54njg47/v2**Version created by **ran cui**

Protocol status: Working
We use this protocol and it's working

Created: April 22, 2024

Last Modified: May 01, 2024

Protocol Integer ID: 98913

Keywords: Immune checkpoint inhibitors; advanced non-small cell lung cancer; objective response rate; adverse events

Abstract

Background: The recent usage of immunotherapy combined with chemoradiotherapy has improved survival in advanced non-small cell lung cancer (NSCLC) patients. However, determining the most effective therapy combination remains a topic of debate. Research suggests immune checkpoint inhibitors (ICIs) post-chemoradiotherapy enhance survival, but the impact of concurrent ICIs during chemoradiotherapy on rapid disease progression is unclear. This meta-analysis aims to assess the effectiveness and safety of concurrent ICIs with radiotherapy or chemoradiotherapy in advanced non-small cell lung cancer.
Methods: We searched PubMed, Embase, the Cochrane Library, and Web of Science for relevant studies, extracting data on overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and adverse events (AEs).
Results: The analysis included ten studies with 490 participants. Stage III NSCLC ORR was 81.8%, while Stage IV ORR was 39.9%. One-year PFS and OS for Stage III were 68.2% and 82.6%, compared to 27.9% and 72.2% for Stage IV. Common adverse events included anemia (46.6%), nausea (47.6%), rash (36.4%), and radiation pneumonitis (36.3%).
Conclusions: Our meta-analysis shows concurrent ICIs with chemoradiotherapy are effective and safe in advanced NSCLC, particularly in stage III patients at risk of progression before starting ICIs after chemoradiotherapy. The findings support further phase III trials. The review protocol was registered on PROSPERO (CRD42023493685) and is detailed on the NIHR HTA programme website.

Attachments

Figures.rar
7.5MB

Supplementary.rar
37.4MB

Date and Statistical...
73KB

Guidelines

1. Study Design: This meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparent and comprehensive reporting of the study methods and results.
2. Literature Search: A comprehensive literature search will be conducted using multiple electronic databases (PubMed, Embase, Cochrane Library, and Web of Science) to identify all relevant studies. The search strategy will be developed in consultation with a medical librarian and will include a combination of MeSH terms and free-text keywords.
3. Study Selection: Two independent reviewers will screen the titles and abstracts of the retrieved articles for relevance. Full-text articles will be assessed for eligibility based on the predefined inclusion and exclusion criteria. Any discrepancies will be resolved through discussion or consultation with a third reviewer.
4. Data Extraction: Two independent reviewers will extract data from the included studies using a standardized data extraction form. The extracted data will include study characteristics (e.g., author, year, study design, sample size), patient demographics, treatment details (e.g., type of ICI, radiotherapy dose, chemotherapy regimen), and outcomes (e.g., ORR, PFS, OS, AEs).
5. Quality Assessment: The quality of the included studies will be assessed using appropriate tools based on the study design. The Cochrane Risk of Bias Tool will be used for randomized controlled trials, while the Newcastle-Ottawa Scale will be used for non-randomized studies. Two independent reviewers will perform the quality assessment, and discrepancies will be resolved through discussion.
6. Statistical Analysis: The meta-analysis will be conducted using a random-effects model to account for heterogeneity among the included studies. Heterogeneity will be assessed using the I^2 statistic and Cochran's Q test. Subgroup analyses will be performed based on factors such as tumor stage, type of ICI, and type of radiotherapy. Sensitivity analyses will be conducted to evaluate the robustness of the results. Publication bias will be assessed using funnel plots and Egger's test.
7. Interpretation of Results: The results of the meta-analysis will be interpreted in the context of the available evidence and the limitations of the included studies. The clinical implications of the findings will be discussed, and recommendations for future research will be provided.

Materials

Search Strategy

Four databases – PubMed, Embase, the Cochrane Library, and Web of Science – were thoroughly searched for pertinent studies. The final search date was 4 January 2024. The search strategy incorporated both MeSH terms and free-text words: "concurrent radiotherapy" OR "concurrent radiation therapy" OR "concurrent chemoradiotherapy" OR "concurrent radiotherapy AND immunotherapy" OR "concurrent chemoradiotherapy AND immunotherapy" AND ("immune checkpoint inhibitors" OR "PD-1 inhibitors" OR "PD-L1 inhibitors" OR "CTLA-4 inhibitors" OR "immune modulation" OR "immunotherapy") AND "advanced NSCLC" OR "advanced non-small cell lung cancer". Searches were restricted to English language publications. Additionally, the references of the included articles were reviewed to identify further relevant studies.

Selection Criteria

Studies were included in this meta-analysis if they met the following inclusion criteria: 1) population: patients diagnosed with advanced non-small cell lung cancer (NSCLC); and 2) intervention: patients treated with concurrent immune checkpoint inhibitors (ICIs) combined with radiotherapy/chemoradiotherapy. Study Type: Prospective interventional research, retrospective analyses, or randomized controlled trials (RCTs). 3) Outcomes: Clinical tumor outcomes of interest, including objective response rate (ORR), one-year progression-free survival (PFS), one-year overall survival (OS), and adverse events (AEs), were reported. 4) Tumor responses were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) [19], version 1.1. Toxic effects were assessed for incidence and severity using the Common Terminology Criteria for Adverse Events (CTCAE). The exclusion criteria were as follows: Animal-related studies, cell studies, reviews, meta-analyses, duplicates, case reports, or letters.

Two investigators independently screened the articles for eligibility using the inclusion and exclusion criteria. Any disagreements regarding study selection were resolved by discussion between the two investigators or with the involvement of a third investigator.

Data Extraction and Quality Assessment

Data from all included studies were independently extracted by two investigators, who also conducted a quality assessment of the studies. The extracted data included author name, publication year, study type, sample size, intervention, tumor stage, median follow-up time, EGFR mutation status, and reported endpoints. Clinical and safety outcomes were evaluated based on the overall response rate (ORR), one-year overall survival (OS), one-year progression-free survival (PFS), incidence of any adverse events (AEs), and incidence of grade 3 or higher AEs.

Furthermore, the quality of the included randomized controlled trials (RCTs) was assessed using the Jadad scale, while the retrospective studies were evaluated using the Joanna Briggs Institute Critical Appraisal Checklist for Patient Series. The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of the included noncontrolled trials.

Statistical Analysis

This meta-analysis was conducted using STATA 17 software (StataCorp LP, College Station, TX, United States) to analyze the data. Heterogeneity among studies was assessed with the chi-square test and I2 statistic, with p values less than 0.1 denoting significant differences. In cases where there was significant variability ($p < 0.1$ and $I2 > 50\%$), the analysis utilized a random effects approach. On the other hand, for scenarios with lower variability, a fixed-effects approach was chosen. Additionally, sensitivity analyses were conducted to assess the robustness

and reliability of the findings. The potential for publication bias was examined through the application of Begg's and Egger's tests.

Safety warnings

1. Adverse Events: Combining immune checkpoint inhibitors with radiotherapy or chemoradiotherapy may increase the risk of adverse events, particularly immune-related adverse events (irAEs) such as pneumonitis, colitis, and endocrinopathies . Patients should be closely monitored for signs and symptoms of irAEs, and prompt management should be initiated according to established guidelines .
2. Radiation Dose and Volume: The radiation dose and volume should be carefully considered when combining radiotherapy with immune checkpoint inhibitors, as higher doses and larger volumes may increase the risk of toxicity . The optimal radiation dose and fractionation schedule for use with immune checkpoint inhibitors are still under investigation, and caution should be exercised when deviating from established protocols.
3. Timing of Immune Checkpoint Inhibitor Administration: The timing of immune checkpoint inhibitor administration relative to radiotherapy or chemoradiotherapy may impact the efficacy and safety of the combination . While concurrent administration has shown promise in some studies, it may also increase the risk of adverse events. The optimal timing of immune checkpoint inhibitor administration should be based on available evidence and patient-specific factors.
4. Patient Selection: Careful patient selection is crucial when combining immune checkpoint inhibitors with radiotherapy or chemoradiotherapy, as certain patient populations may be at higher risk of adverse events. Patients with pre-existing autoimmune disorders, prior history of severe irAEs, or compromised organ function should be evaluated on a case-by-case basis, and the potential benefits of the combination should be weighed against the risks .
5. Long-term Follow-up: As the use of immune checkpoint inhibitors in combination with radiotherapy or chemoradiotherapy is a relatively new approach, long-term follow-up data on the safety and efficacy of these combinations are limited . Patients should be informed of the potential for late-onset adverse events and the need for ongoing monitoring even after the completion of treatment.

Ethics statement

This meta-analysis was conducted in accordance with the Declaration of Helsinki. All included studies had obtained informed consent from their participants and were approved by their respective institutional ethics committees. As this study is a meta-analysis of previously published data, no additional informed consent was required.

Before start

Protocol Registration: The study protocol should be registered in a publicly accessible database, such as PROSPERO (International Prospective Register of Systematic Reviews) or the Open Science Framework (OSF), to promote transparency and reduce duplication of efforts.

Search Strategy Development: The search strategy should be developed in consultation with a medical librarian or an information specialist to ensure that it is comprehensive and captures all relevant studies. The search strategy should be peer-reviewed using the Peer Review of Electronic Search Strategies (PRESS) checklist [23] to minimize errors and improve its effectiveness.

Data Management: A data management plan should be established before starting the study to outline how data will be collected, stored, and shared. This plan should include measures to ensure data security, confidentiality, and access control. The use of a secure, cloud-based platform, such as REDCap (Research Electronic Data Capture) [24], can facilitate efficient and secure data management.

Study Protocol: The study protocol should be developed following the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines to ensure that all essential elements are included. The protocol should be reviewed and approved by all members of the research team before the start of the study.

Authorship and Collaboration: The roles and responsibilities of each member of the research team should be clearly defined, and authorship criteria should be established in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines . If the meta-analysis involves collaboration with external partners or institutions, data sharing agreements and memoranda of understanding should be established to ensure smooth collaboration and protect intellectual property rights.

Training and Calibration: All members of the research team should receive appropriate training on the study protocol, data extraction, quality assessment, and statistical analysis methods to ensure consistency and minimize errors. Calibration exercises should be conducted to assess inter-rater reliability and resolve any discrepancies in the interpretation of the study criteria.

steps

1 Develop a research question and hypothesis:Clearly define the research question and hypothesis for the meta-analysis, focusing on the efficacy and safety of concurrent immune checkpoint inhibitors combined with radiotherapy or chemoradiotherapy for advanced non-small cell lung cancer.

2 Register the protocol: Register the study protocol in a publicly accessible database, such as PROSPERO or the Open Science Framework, to promote transparency and reduce duplication of efforts.

3 Develop a search strategy: In consultation with a medical librarian or information specialist, develop a comprehensive search strategy that captures all relevant studies. Peer-review the search strategy using the PRESS checklist.

4 Conduct a literature search: Search multiple electronic databases (PubMed, Embase, Cochrane Library, and Web of Science) using the developed search strategy to identify all relevant studies.

5 Screen and select studies: Two independent reviewers should screen the titles and abstracts of the retrieved articles for relevance. Assess full-text articles for eligibility based on the predefined inclusion and exclusion criteria. Resolve any discrepancies through discussion or consultation with a third reviewer.

6 Extract data: Two independent reviewers should extract data from the included studies using a standardized data extraction form. Extract study characteristics, patient demographics, treatment details, and outcomes.

7 Assess study quality: Assess the quality of the included studies using appropriate tools based on the study design (e.g., Cochrane Risk of Bias Tool for randomized controlled trials, Newcastle-Ottawa Scale for non-randomized studies). Two independent reviewers should perform the quality assessment and resolve discrepancies through discussion.

8 Conduct statistical analysis: Perform meta-analysis using a random-effects model to account for heterogeneity among the included studies. Assess heterogeneity using the I^2 statistic and Cochran's Q test. Perform subgroup analyses based on factors such as tumor stage, type of ICI, and type of radiotherapy. Conduct sensitivity analyses to evaluate the robustness of the results. Assess publication bias using funnel plots and Egger's test.

9 Interpret results: Interpret the results of the meta-analysis in the context of the available evidence and the limitations of the included studies. Discuss the clinical implications of the findings and provide recommendations for future research.

10 Draft the manuscript: Write the manuscript following the PRISMA guidelines, including all essential elements such as the abstract, introduction, methods, results, discussion, and

conclusion. Ensure that the manuscript adheres to the journal's formatting and submission requirements.

11 Review and revise: Circulate the draft manuscript among all authors for review and feedback. Revise the manuscript based on the comments and suggestions received.

12 Submit for publication: Submit the final manuscript to the target journal and respond to any reviewer comments or editorial requests during the peer-review process.

Protocol references

1. Cancer.Net Editorial Board. Lung cancer - non-small cell: statistics, 2023. Available from: https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics
2. Mithoowani H, Febbraro M. Non-small-cell lung cancer in 2022: A review for general practitioners in oncology. Curr Oncol. 2022;29: 1828-39. doi: 10.3390/curroncol29030150
3. Jasper K, Stiles B, McDonald F, Palma DA. Practical management of oligometastatic non–small-cell lung cancer. J Clin Oncol. 2022;40: 635-41. doi: 10.1200/jco.21.01719
4. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol. 2010;28: 2181-90. doi: 10.1200/jco.2009.26.2543
5. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387: 1540-50. doi: 10.1016/s0140-6736(15)01281-7
6. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. 2019;393: 1819-30. doi: 10.1016/s0140-6736(18)32409-7
7. Ettinger DS, Wood DE, Akerley W, Bazhenova LA, Borghaei H, Camidge DR, et al. NCCN guidelines insights: non–small cell lung cancer, version 4.2016. J Natl Compr Canc Netw. 2016;14: 255-64. doi: 10.6004/jnccn.2016.0031
8. Spigel DR, Faivre-Finn C, Gray JE, Vicente D, Planchard D, Paz-Ares L, et al. Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. J Clin Oncol. 2022;40: 1301-11. doi: 10.1200/jco.21.01308
9. Wu J, Ni T, Deng R, Li Y, Zhong Q, Tang F, et al. Safety and efficacy of radiotherapy/chemoradiotherapy combined with immune checkpoint inhibitors for non-small cell lung cancer: A systematic review and meta-analysis. Front Immunol. 2023;14: 1065510. doi: 10.3389/fimmu.2023.1065510
10. Zhang Y, Tian Y, Zheng L, Sun X, Zhao Z, Zheng Y, et al. Efficacy and safety of consolidation durvalumab after chemoradiation therapy for stage III non-small-cell lung cancer: a systematic review, meta-analysis, and meta-regression of real-world studies. Front Pharmacol. 2023;14: 1103927. doi: 10.3389/fphar.2023.1103927
11. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. N Engl J Med. 2017;377: 1919-29. doi: 10.1056/NEJMoa1709937
12. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, et al. NCCN guidelines® insights: Non-small cell lung cancer, version 2.2023. J Natl Compr Canc Netw. 2023;21: 340-50. doi: 10.6004/jnccn.2023.0020
13. Xuan L, Bai C, Ju Z, Luo J, Guan H, Zhou PK, et al. Radiation-targeted immunotherapy: A new perspective in cancer radiotherapy. Cytokine Growth Factor Rev. 2023. doi: 10.1016/j.cytogfr.2023.11.003
14. Brandmaier A, Formenti SC. The impact of radiation therapy on innate and adaptive tumor immunity. Semin Radiat Oncol. 2020;30: 139-44. doi: 10.1016/j.semradonc.2019.12.005
15. Procureur A, Simonaggio A, Bibault JE, Oudard S, Vano YA. Enhance the immune checkpoint inhibitors efficacy with radiotherapy induced immunogenic cell death: A comprehensive review and latest developments. Cancers (Basel). 2021;13. doi: 10.3390/cancers13040678
16. Davar D, Zarour HM. Immunological targets for immunotherapy: inhibitory T cell receptors. Methods Mol Biol. 2020;2055: 23-60. doi: 10.1007/978-1-4939-9773-2_2

17. Du SS, Chen GW, Yang P, Chen YX, Hu Y, Zhao QQ, et al. Radiation therapy promotes hepatocellular carcinoma immune cloaking via PD-L1 upregulation induced by cGAS-STING activation. Int J Radiat Oncol Biol Phys. 2022;112: 1243-55. doi: 10.1016/j.ijrobp.2021.12.162
18. Galluzzi L, Aryankalayil MJ, Coleman CN, Formenti SC. Emerging evidence for adapting radiotherapy to immunotherapy. Nat Rev Clin Oncol. 2023;20: 543-57. doi: 10.1038/s41571-023-00782-x
19. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45: 228-47. doi: 10.1016/j.ejca.2008.10.026
20. Abe T, Iino M, Saito S, Aoshika T, Ryuno Y, Ohta T, et al. Comparison of the efficacy and toxicity of concurrent chemoradiotherapy and durvalumab and concurrent chemoradiotherapy alone for locally advanced non-small cell lung cancer with N3 lymph node metastasis. Anticancer Res. 2023;43: 675-82. doi: 10.21873/anticanres.16205
21. Akamatsu H, Murakami H, Harada H, Shimizu J, Hayashi H, Daga H, et al. Gefitinib with concurrent thoracic radiotherapy in unresectable locally advanced NSCLC with EGFR mutation; West Japan Oncology Group 6911L. J Thorac Oncol. 2021;16: 1745-52. doi: 10.1016/j.jtho.2021.05.019
22. Bestvina CM, Pointer KB, Karrison T, Al-Hallaq H, Hoffman PC, Jelinek MJ, et al. A phase 1 trial of concurrent or sequential ipilimumab, nivolumab, and stereotactic body radiotherapy in patients with stage IV NSCLC study. J Thorac Oncol. 2022;17: 130-40. doi: 10.1016/j.jtho.2021.08.019
23. Liu Y, Yao L, Kalhor N, Carter BW, Altan M, Blumenschein G, et al. Final efficacy outcomes of atezolizumab with chemoradiation for unresectable NSCLC: The phase II DETERRED trial. Lung Cancer. 2022;174: 112-7. doi: 10.1016/j.lungcan.2022.10.006
24. Welsh J, Menon H, Chen D, Verma V, Tang C, Altan M, et al. Pembrolizumab with or without radiation therapy for metastatic non-small cell lung cancer: a randomized phase I/II trial. J Immunother Cancer. 2020;8. doi: 10.1136/jitc-2020-001001
25. Tachihara M, Tsujino K, Ishihara T, Hayashi H, Sato Y, Kurata T, et al. Durvalumab plus concurrent radiotherapy for treatment of locally advanced non-small cell lung cancer: The DOLPHIN phase 2 nonrandomized controlled trial. JAMA Oncol. 2023;9: 1505-13. doi: 10.1001/jamaoncol.2023.3309
26. Jabbour SK, Berman AT, Decker RH, Lin Y, Feigenberg SJ, Gettinger SN, et al. Phase 1 trial of Pembrolizumab administered concurrently with Chemoradiotherapy for locally advanced non–small cell lung cancer: a nonrandomized controlled trial. JAMA Oncol. 2020;6: 848-55. doi: 10.1001/jamaoncol.2019.6731
27. Peters S, Felip E, Dafni U, Tufman A, Guckenberger M, Álvarez R, et al. Progression-free and overall survival for concurrent nivolumab with standard concurrent chemoradiotherapy in locally advanced stage IIIA-B NSCLC: results from the European Thoracic Oncology Platform NICOLAS Phase II Trial (European Thoracic Oncology Platform 6-14). J Thorac Oncol. 2021;16: 278-88. doi: 10.1016/j.jtho.2020.10.129
28. Tang S, Cong X, Zheng D, Chen C, Liu Z, Gao J, et al. Concurrent sintilimab with sequential chemoradiotherapy for unresectable, stage III non-small cell lung cancer: a retrospective study. Front Oncol. 2023;13: 1129989. doi: 10.3389/fonc.2023.1129989
29. Jabbour SK, Lee KH, Frost N, Breder V, Kowalski DM, Pollock T, et al. Pembrolizumab plus concurrent chemoradiation therapy in patients with unresectable, locally advanced, stage III non–small cell lung cancer: The phase 2 KEYNOTE-799 nonrandomized trial. JAMA Oncol. 2021;7: 1-9. doi: 10.1001/jamaoncol.2021.2301
30. Denault MH, Feng J, Kuang S, Shokoohi A, Leung B, Liu M, et al. Beyond PACIFIC: Real-world outcomes of adjuvant durvalumab according to treatment received and PD-L1 expression. Curr Oncol. 2023;30: 7499-507. doi: 10.3390/curroncol30080543

31. Bruni A, Scotti V, Borghetti P, Vagge S, Cozzi S, D'Angelo E, et al. A real-world, multicenter, observational retrospective study of durvalumab after concomitant or sequential chemoradiation for unresectable stage III non-small cell lung cancer. Front Oncol. 2021;11: 744956. doi: 10.3389/fonc.2021.744956
32. Desilets A, Blanc-Durand F, Lau S, Hakozaki T, Kitadai R, Malo J, et al. Durvalumab therapy following chemoradiation compared with a historical cohort treated with chemoradiation alone in patients with stage III non-small cell lung cancer: A real-world multicentre study. Eur J Cancer. 2021;142: 83-91. doi: 10.1016/j.ejca.2020.10.008
33. Conibear J. Rationale for concurrent chemoradiotherapy for patients with stage III non-small-cell lung cancer. Br J Cancer. 2020;123: 10-7. doi: 10.1038/s41416-020-01070-6
34. Guan S, Ren K, Zhang X, Yan M, Li X, Zhao L. Concurrent chemoradiotherapy versus radiotherapy alone after induction chemoimmunotherapy for stage III NSCLC patients who did not undergo surgery: a single institution retrospective study. Radiat Oncol. 2023;18: 122. doi: 10.1186/s13014-023-02305-5
35. Kashihara T, Nakayama Y, Okuma K, Takahashi A, Kaneda T, Katagiri M, et al. Impact of interstitial lung abnormality on survival after adjuvant durvalumab with chemoradiotherapy for locally advanced non-small cell lung cancer. Radiother Oncol. 2023;180: 109454. doi: 10.1016/j.radonc.2022.109454
36. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. N Engl J Med. 2018;378: 2078-92. doi: 10.1056/NEJMoa1801005
37. Wu L, Zhang Z, Bai M, Yan Y, Yu J, Xu Y. Radiation combined with immune checkpoint inhibitors for unresectable locally advanced non-small cell lung cancer: synergistic mechanisms, current state, challenges, and orientations. Cell Commun Signal. 2023;21: 119. doi: 10.1186/s12964-023-01139-8
38. Avrillon V, Daniel C, Boisselier P, et al. Nationwide real-life safety and treatment exposure data on durvalumab after concurrent chemoradiotherapy in unresectable stage III, locally advanced, non-small cell lung cancer: analysis of patients enrolled in the French Early Access Program[J]. Lung, 2022, 200(1): 95-105.
39. Preti B T B, Sanatani M S, Breadner D, et al. Real-World Analysis of Durvalumab after Chemoradiation in Stage III Non-Small-Cell Lung Cancer[J]. Current Oncology, 2023, 30(8): 7713-7721.
40. Ellison C, Martens M, Argote J A, et al. High-grade pneumonitis events in unresectable, locally advanced non-small cell lung cancer patients treated with definitive chemoradiation followed by adjuvant durvalumab[J]. JTO Clinical and Research Reports, 2023: 100537.
41. Guberina N, Wirsdörfer F, Stuschke M, et al. Combined radiation-and immune checkpoint-inhibitor-induced pneumonitis–The challenge to predict and detect overlapping immune-related adverse effects from evolving laboratory biomarkers and clinical imaging[J]. Neoplasia, 2023, 39: 100892.
42. Chen Y, Gao M, Huang Z, et al. SBRT combined with PD-1/PD-L1 inhibitors in NSCLC treatment: a focus on the mechanisms, advances, and future challenges[J]. Journal of hematology & oncology, 2020, 13: 1-17
43. Zayed S, Louie A V, Breadner D A, et al. Radiation and immune checkpoint inhibitors in the treatment of oligometastatic non-small-cell lung cancer: a practical review of rationale, recent data, and research questions[J]. Therapeutic Advances in Medical Oncology, 2023, 15: 17588359231183668.
44. Weichselbaum R R, Liang H, Deng L, et al. Radiotherapy and immunotherapy: a beneficial liaison?[J]. Nature reviews Clinical oncology, 2017, 14(6): 365-379.
45. Janopaul-Naylor J R, Shen Y, Qian D C, et al. The abscopal effect: a review of pre-clinical and clinical advances[J]. International journal of molecular sciences, 2021, 22(20): 11061
46. Dovedi S J, Adlard A L, Lipowska-Bhalla G, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade[J]. Cancer research, 2014, 74(19): 5458-5468.

47. Twyman-Saint Victor C, Rech A J, Maity A, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer[J]. Nature, 2015, 520(7547): 373-377