Peer Review File

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Reviewer A

Comment 1: -There are a number of biases in this study that affect the interpretation of this study. Such as why were patients treated with IO vs chemo ->? pace of disease, PDL1 status, ECOG, access to drug; all which influence the study findings.

Reply 1: Thank you for the comment. Please see **Table 2** In the multivariate analysis, we have adjusted for a variety of patient and tumor characteristics including age at diagnosis, sex, race, ethnicity, marital status at diagnosis, patient's residence rurality, census tract-level poverty level, tumor characteristics (metastasis, tumor grade, histology, size), cranial surgery and radiation information, as well as Charlson Comorbidity Index and a proxy ECOG measure. Since we are examining NSCLC patients with brain metastases at diagnosis, all patients had distant cancer. All patients are Medicare enrollees. Coverage for treatment is similar. Unfortunately, we do not have information on patient's PDL1 status. We have provided discussion of this limitation in the "Strength and Limitation" section. To overcome this limitation, we used a historical cohort of patients who received subsequent chemotherapy treatment before 2015, the year when the FDA first approved ICIs as a subsequent treatment for NSCLC, as the comparison group. This cohort did not have access to ICIs at the time of the subsequent treatment decision and therefore included patients with any level of PDL-1. Please see the "Strength and Limitation" section on page 12, lines 295 – 300.

Changes in the text: No changes.

Comment 2: -Also, no mention was made if driver mutation testing was carried out in all patients. In the study period NGS and ctDNA were not in wide use. This should be discussed

Reply 2: Thank you for this insightful comment. We have added this to the limitation section.

Changes in the text: Added "We also do not have information on the driver mutation testing results, which were not in wide use at the time period for this study and therefore was not likely a consideration for physician's treatment choice between ICI and chemotherapy." to the "Strength and Limitation" section (page 12, line 300-302)

Comment 3: -The study period mentioned by the authors was when ICI were being introduced in the treatment paradigm of NSCLC. Now patients with brain mets are usually treated with 1L IO+/-chemo, so the findings of study not be relevant in current practice

Reply 3: Thank you for this insightful comment. These treatments have been studied mainly in melanoma patients with brain metastases, but are still being studied in other tumor types. Most of the trials are for first-line use, with only a few trials for subsequent-line use (Wang et al., 2021). Because of the small number of patients with brain metastasis in the subsequent-line trials, the results are inconclusive (Wang et al., 2021). Our study used real-world data and focused exclusive on elderly patients 65+, who are underrepresented in the trials and often in poorer general condition than those included in the trials. Therefore, we believe our study still provides valuable information and can assist the physicians in making subsequent treatment decisions, particularly for older patients who are refractory to chemotherapy.

Wang Y, Zhang Q, Chen C, Hu Y, Miao L, Zhou Y. Association of Brain Metastases With Immune Checkpoint Inhibitors Efficacy in Advanced Lung Cancer: A Systematic Review and Meta-Analysis. Front Oncol. 2021 Dec 8;11:721760. doi: 10.3389/fonc.2021.721760. PMID: 34956860; PMCID: PMC8694212.

Changes in the text: No changes

Reviewer B

Comment 1: 81- US - it is worth developing the abbreviation
Reply 1: Thank you for pointing this out. Changes have been made in the text.
Changes in the text: We have introduced the abbreviation "US" on page 5, line 80 and used the abbreviation afterwards.

Comment 2: 214-AIC,SBC- it is worth developing the abbreviation
Reply 2: Thank you for pointing this out. Changes have been made in the text.
Changes in the text: Occurrences of AIC and SBC on page 9 line 201-202 have been changed to "Akaike's Information Criterion and Schwartz's Bayesian Criterion".

Comment 3: 218-CCI- it is worth developing the abbreviation
Reply 3: Thank you for pointing this out. Changes have been made in the text.
Changes in the text: We have first introduced the Charlson Comorbidity Index, abbreviated as "CCI" on Page 8, line 174 and used the abbreviation afterwards.

Comment 4: 235- -maybe it's worth paying attention to- the most common diagnosis was adenocarcinoma
Reply 4: Thank you for bringing this to our attention. The text has been updated.
Changes in the text: On page 10, lines 220-221, we revised the sentence as following, "Majority of patients in both groups had adenocarcinoma (63.37% vs. 62.64%); however, patients receiving ICI treatment were more likely to have squamous cell carcinoma (16.85% vs. 9.16%, p=0.0099) compared to the chemotherapy group, but similar concerning all other covariates."

Comment 5: 282- results obtained in table 1-cranial radiation before index treatment and neurosurgical resection within 1 year from diagnosis. In the group with brain radiotherapy 165 patients were treated with ICI, without brain radiotherapy 108 patients were treated with ICI. After neurosurgical surgery, 50 patients were treated with ICI.
I wonder if patients after brain radiotherapy or neurosurgery responded better to ICI?
Reply 5: Thank you for this insightful comment. Please see **Table 2** and **Supplemental Table S5**. **Table 2** reports our main analysis results which included all patients in this study. The adjusted HR for patients received cranial radiation before subsequent systemic treatment (ICI or chemotherapy) was statistically significant (HR, 95% CI: 0.64, 0.42-0.96; P=0.0300), indicating a lower risk comparing to patients who did not receive cranial radiation before subsequent systemic treatment. The HR for receiving neurosurgical resection within one year of diagnosis was negative but not statistically significant (HR, 95% CI: 0.82, 0.64-1.06;

P=0.1313). Since patients in this study all had distant lung cancer, surgical resection of the brain tumor(s) was only conditionally recommended if the tumor is large and produce significant symptoms (Gondi et al, 2022). As can be seen from **Table 1**, only about 18% of patients in both groups received cranial surgery (p=0.9116). These results indicated that patients who received cranial radiation before subsequent treatment (ICI or chemotherapy) had better survival. But neurosurgery within one year of diagnosis did not significantly affect survival after adjusting for other patient and tumor characteristics. (**Table 2**). In **Supplemental Table S5**, we reported the sensitivity analysis restricting to patients who received cranial radiation before subsequent treatment (i.e. a subgroup of patients who all received cranial radiation before subsequent treatment). **Table 1** shows that about 61% of patients in both groups received cranial radiation before subsequent treatment and there was no difference between subsequent ICI and chemotherapy groups (p=0.6317). In **Supplemental Table S5**, we found that subsequent use of ICI had a similar survival benefit over chemotherapy in the subgroup of patients who all received cranial radiation before (HR, 95% CI: 0.65, 0.51-0.82; P=0.0004) as in the main analysis where we included all patients (i.e. regardless of whether they received cranial radiation before (see **Table** 2, HR, 95% CI: 0.63, 0.51-0.75; P=<0.0001). These findings indicated that cranial radiation improves survival in all patients and does not significantly attenuate the responses to ICI.

Gondi, V., Bauman, G., Bradfield, L., Burri, S. H., Cabrera, A. R., Cunningham, D. A., ... & Brown, P. D. (2022). Radiation therapy for brain metastases: an ASTRO clinical practice guideline. Practical radiation oncology, 12(4), 265-282.

Changes in the text: No changes.

Comment 6: In table 2, supplemental tables S2,S3 and S5- neurosurgical resection within 1 year of diagnosis, cranial radiation before index treatment date : hazard ratios of overall survival was below 1.

Reply 6: Thank you for pointing this out. Please also see results in **Table 2**, our main analysis. The supplemental tables reported the sensitivity analyses where we used different statistical approaches (**Supplemental Tables S2, S3, S4**) or a more restricted patient subgroup (**Supplemental Table** S5, excluding those without cranial radiation before subsequent treatment). The findings are generally consistent. Please also see our response to Reviewer B's Comment 5 above.

Changes in the text: No changes**.**

Comment 7: The blood-brain barrier (BBB) is a term used to describe the strengthened microvascular network of the central nervous system, known for its extremely increased molecular specificity – facilitating providing nutrients while hindering the access of harmful substances to the brain. Radiotherapy by damaging the blood-brain barrier facilitates the penetration of drugs.

Reply 7: Thank you for this valuable comment.

Changes in the text: No changes.

Comment 8: This study is very important, deals with elderly patients, often in poor general condition. The presented treatment results regarding the use of ICIs are favorable for this group of drugs, especially since they concern the 2nd and 3rd lines of treatment.

Reply 8: Thank you for this comment. We agree with the reviewer that the patient cohort we studied represent an important group of patients that are often underrepresented in clinical trials and believe our study findings has important clinical implication.

Changes in the text: No changes.