Peer Review File

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Reviewer A

The efficacy of pemetrexed (PEM) as adjuvant chemotherapy after surgery is highly anticipated in the future, and the value and impact of this manuscript are significant. I believe it is well worth publication. I would like to point out the following issues for the authors' consideration:

Since the genetic mutation analysis was likely not performed using a comprehensive gene panel test, the authors should mention this limitation — namely, that exhaustive genomic profiling was not conducted.

Reply 1: Thank you for this valuable comment. In the present study, next-generation sequencing (NGS) was performed for all patients in the prospective PEM group; however, the retrospective non-PEM group did not undergo comprehensive genetic profiling. This approach may have resulted in the omission of potential driver gene mutations that could influence survival outcomes. We have explicitly acknowledged this limitation in the revised Discussion section, noting that exhaustive genomic profiling was not conducted. Furthermore, we added that future studies incorporating systematic genetic testing will be valuable for elucidating the molecular determinants of treatment response.
Changes in the text: Page 12, line286-290

The key value of this manuscript appears to lie in the evaluation of adjuvant chemotherapy using PEM-based regimens, particularly for patients without driver mutations. Therefore, I recommend including a subgroup analysis limited to the mutation-negative group, along with Kaplan–Meier curves, to further demonstrate the utility of PEM in this context.

Reply 2: Thank you for this insightful suggestion. However, due to the lack of EGFR mutation data in the non-PEM group, we were unable to compare survival outcomes among EGFR wild-type patients across different postoperative adjuvant treatment regimens. However, we supplemented the analysis with an exploratory investigation into the impact of EGFR mutation status on DFS within the PEM group. Your comment has highlighted an important direction for future research, suggesting that well-designed randomized controlled trial (RCT) could be conducted to evaluate the potential superiority of pemetrexed plus platinum chemotherapy over other platinum-doublet regimens in patients with driver-gene negative, surgically resected lung adenocarcinoma.
Changes in the text: Page9, line209-216; Page 12, line286-302

It is also desirable to include a description of how folic acid and vitamin B12 supplementation — commonly used to prevent adverse effects during PEM administration — was managed in this study.

Reply 3: Thank you for this reminder. We have now supplemented the Methods section with a detailed description of the administration for folic acid and vitamin B12 throughout the pemetrexed treatment course.
Changes in the text: Page 7, line138-143

Reviewer B

General Comment

This manuscript evaluates the efficacy and safety of pemetrexed plus platinum as postoperative adjuvant chemotherapy for stage II–IIIA lung adenocarcinoma, using a historical cohort as the comparator. The topic is clinically important, and the authors report a significant improvement in disease-free survival (DFS) as well as a more favorable toxicity profile with pemetrexed-based regimens. However, several methodological and interpretative issues need to be addressed before the manuscript can be considered for publication.

Major Comments

1. Study Objective and Rationale

The Introduction would benefit from a clearer statement of the study's rationale. In particular, the authors should explicitly explain why pemetrexed was chosen for adenocarcinoma cases and how this choice addresses the current treatment gaps, despite advances in adjuvant immunotherapy and targeted therapy.

Reply 1: Thank you for this valuable suggestion. We have now revised the Introduction to provide a clearer rationale for focusing on pemetrexed-based adjuvant chemotherapy. Specifically, we explain that pemetrexed has demonstrated favorable efficacy and safety in non-squamous NSCLC, and optimizing chemotherapy remains important given that adjuvant immunotherapy and targeted therapy are only applicable to selected patient subgroups particularly those with driver-gene wild-type disease or low PD-L1 expression.

Changes in the text: Page4-5, line72-80; page5, line91-95

2. Interpretation of Existing Evidence (JIPANG Trial)

The manuscript refers to a "lack of strong evidence," but the JIPANG trial was a phase III randomized controlled study demonstrating non-inferiority of cisplatin plus pemetrexed versus cisplatin plus vinorelbine, with reduced hematologic toxicity. This represents strong evidence. The authors should carefully revise their wording and more accurately position their study within the context of JIPANG and other pivotal trials.

Reply 2: We sincerely thank the reviewer for this important comment. We agree that the JIPANG trial is a pivotal phase III randomized controlled study that has provided strong evidence supporting cisplatin plus pemetrexed as an adjuvant regimen for patients with resected, stage II–IIIA non-squamous NSCLC, demonstrating non-inferiority to cisplatin plus vinorelbine and reduced hematologic toxicity. In light of this comment, we have carefully refined our wording. The phrase "lack of strong evidence" has been removed and replaced in the manuscript to more accurately positions our study within the context of JIPANG and other pivotal trials, while also highlighting the unique contributions of our analysis. Specifically, our study utilized a historical control group treated with non-pemetrexed platinum-based regimens that reflect real-world clinical practice, thereby providing complementary evidence to existing randomized controlled trials.

Changes in the text: Page4-5, line72-80

3. EGFR Mutation Status

Table 1 reports EGFR mutation data for the pemetrexed cohort, but Table 2 (historical control) does not include these data. Given the prognostic and predictive relevance of EGFR mutations, this imbalance may introduce significant bias. The authors should clarify whether EGFR data were unavailable in the historical cohort and discuss the potential impact on the results.

Reply 3: Thank you very much for this valuable suggestion. We have revised the manuscript accordingly. As genetic testing was not routinely performed in the retrospective non-PEM cohort, it was not feasible to compare DFS between EGFR-mutant and wild-type patients across the treatment groups.
To further address this point, we have supplemented our analysis by evaluating the impact of EGFR mutation status on DFS within the prospective PEM cohort. A subgroup analysis of all 71 patients revealed no significant association between EGFR mutation status and DFS ($p = 0.91$, HR = 0.96, 95% CI: 0.50, 1.87). Landmark trials such as ADAURA have demonstrated that EGFR mutations primarily predict benefit from EGFR-targeted agents (e.g., osimertinib). In cohorts where systematic postoperative EGFR-targeted therapy was not implemented, EGFR status may not serve as a significant prognostic factor for the natural history of the disease or response to platinum-based chemotherapy.
We acknowledge, however, that this subgroup analysis is limited by the modest sample size (n=71) and low number of events, which may have resulted in insufficient statistical power to detect a clinically meaningful difference, thereby increasing the risk of a Type II error.
Changes in the text: Page 9, line 209-216; Page 12, line286-302

4. Historical Control Bias
The use of a historical control spanning 2003–2021 may introduce temporal bias related to advances in surgical techniques, diagnostic imaging, and supportive care. Although this is briefly acknowledged in the Discussion, a more thorough treatment of how these factors may have influenced outcomes is necessary.

Reply4: We appreciate the reviewer's insightful comment regarding potential temporal bias introduced by the use of a historical control spanning 2003–2021. We fully agree that advances in surgical techniques, diagnostic imaging, and supportive care over this long period may have influenced outcomes, independent of chemotherapy regimens. In response to this comment, we have expanded the Discussion section to provide a more in-depth analysis of these potential sources of bias. Specifically, we highlight that improvements in perioperative management and staging accuracy may have contributed to the enhanced survival outcomes observed in recent years.
Furthermore, to mitigate baseline imbalances between groups, we applied propensity score matching (PSM), which helped reduce confounding by aligning patient characteristics between the two cohorts as much as possible. Nonetheless, we recognize that PSM cannot fully adjust for the impact of evolving medical practices over time, and we have explicitly acknowledged this as a limitation of our study.
Changes in the text: Page 13, line 307-315

5. Short Follow-up Duration
The median follow-up of the prospective pemetrexed cohort is only 9.2 months. The DFS benefit should therefore be interpreted cautiously. The authors should explicitly acknowledge this limitation and temper their conclusions accordingly.

Reply5: We sincerely thank the reviewer for raising this important concern regarding the limited median follow-up in the prospective pemetrexed cohort. In response, we have recently conducted follow-up of patients in the prospective cohort and updated the dataset with the most recent information. The median follow-up for this cohort has now been extended to 45.6 months (previously 9.2 months). Using the updated follow-up data, we have re-analyzed disease-free survival (DFS), including updated Kaplan–Meier estimates, Cox regression, and propensity score matching (PSM) analyses. The updated results continue to support a DFS benefit in the pemetrexed group.
Changes in the text: Page8,line 185-208

Minor Comments
1. Presentation of Tables
o It would be clearer to present Tables 1 and 2 in a side-by-side comparative format (similar to Table 3), showing both groups together.
Reply: Thank you for your suggestions. The former Table 1 and Table 2 have been merged and are now presented as Table 1.
o A table demonstrating covariate balance before and after propensity score matching (e.g., standardized mean differences) should be added.

Reply: Thank you for your suggestions. The recommended table has now been added to the manuscript labelled as table 3.

2. Figures
The colors of Kaplan–Meier curves are inconsistent (Figure 3A vs Figure 3B). Harmonizing the color scheme would improve readability.

Reply: Thank you so much. We have reperformed the statistical analyses and recreated the tables.

3. Use of Carboplatin
In this study, more than half of the pemetrexed group received carboplatin, whereas the JIPANG trial used cisplatin exclusively. This distinction is clinically relevant and should be highlighted in the Discussion.

Reply: We thank the reviewer for this suggestion. We agree that this point should be interpreted in the Discussion. As multiple recent studies have demonstrated comparable efficacy between cisplatin and carboplatin in lung cancer, along with the superior tolerability and administrative convenience of carboplatin, the vast majority of patients in our prospective cohort received carboplatin-based regimens. Our findings provide complementary real-world evidence to the JIPANG trial.
Changes in the text: Page 12, line 276-285

Conclusion
This study addresses an important clinical question, but the current version requires substantial revision. Clearer articulation of the study rationale, accurate integration of prior evidence, inclusion or discussion of EGFR mutation status in both cohorts, and fuller acknowledgment of design limitations will significantly strengthen the manuscript.