Peer Review File

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Reviewer A

▪ Comment 1

I would add the following paper to the References list.
Santarpia, M., Altavilla, G., Borsellino, N., Girlando, A., Mancuso, G., Pergolizzi, S., Piazza, D., Pontoriero, A., Valerio, M. R., & Gebbia, V. (2020). High-dose Radiotherapy for Oligo-progressive NSCLC Receiving EGFR Tyrosine Kinase Inhibitors: Real World Data. In vivo (Athens, Greece), 34(4), 2009–2014. https://doi.org/10.21873/invivo.11999

▪ Reply 1

Thank you for your suggestion. The paper you have recommended supports the use of local ablative approaches in patients with oligo-progressive EGFR-mutated NSCLC, and it is already included as Reference 14 (see Page 3, lines 71 to 73, and References list number 14).

Reviewer B

▪ Comment 1

Line 65-66: "The progression frees survival of "First line EGFR TKI" was 9-13 months." Do the authors refer to 1st generation 1st line EGFR TKI only? Dacomatinib and Osimertinib give better PFS but can also be used as 1st line EGFR TKI therapy. The authors should be more specific in this statement.

▪ Reply 1

Thank you for your comment. We agree that the description "However, the emergence of acquired resistance, which leads to disease progression within 9–13 months after treatment with first-line EGFR-TKIs" could be confusing to the reader, especially considering that dacomitinib and osimertinib demonstrated median PFS of 14.6 and 18.9 months, respectively (1,2). The EGFR-TKIs analyzed in our study were all 1st or 2nd generation (gefitinib, erlotinib, icotinib, and afatinib), and their median PFS were referenced. To clarify that disease progression due to the emergence of acquired resistance can occur when using EGFR-TKIs as first-line therapy, we have made the following revision (see Page 3, lines 65 to 66):

▪ Changes in the text

Page 3, lines 65 to 66
However, the emergence of acquired resistance, which leads to disease progression ~~within 9–13 months~~ after treatment with first-line EGFR-TKIs, has limited the potential benefits to survival (7-9).

References
1. Ann Oncol. 2016;27:423-9.
2. N Engl J Med. 2018;378:113-125.

▪ Comment 2

Line 162: Ref 36 is not a RCT. It was a phase II single arm prospective study. The comparison made was the screen failure subjects who did not receive radiation.

▪ Reply 2

Thank you for pointing this out. While re-evaluating the included studies, we discovered our mistake. The study by Chan et al. was not an RCT but a phase II single-arm prospective study. The comparison group consisted of subjects who failed screening with four or more metabolically avid residuals (defined as maximum SUV >2.5) on the PET-CT scan. Consequently, we have revised the related content as follows (see Page 5, lines 161 to 163, Page 7, lines 258 to 259, the fourth row of the second column in Table 1, and supplementary figure S1):

▪ **Changes in the text**

Page 5, lines 161 to 163

Among the 11 final studies, which covered 1,313 patients, two were RCTs (n = 194) (44,45), one was a phase II single-arm prospective study (n = 59) (37), and eight were retrospective case-control studies (n = 1,060) (35,36,38-43).

Page 7, lines 258 to 259

Second, although RCTs are considered the gold standard for evaluating intervention efficacy, this study had access to only two RCTs.

▪ **Comment 3**

Line 192: How to classify or define “late” versus “early” LT?

▪ **Reply 3**

We agree that the definition for distinguishing between “late” and “early” LT is not clear. As mentioned in the discussion, there is currently no established standard for the optimal timing of LT. Performing LT after the maximal response to EGFR-TKIs is anticipated to have benefits, such as reducing the extent of LT. Moreover, as you mentioned in Comment 5, EGFR-TKI therapy may transition polymetastatic disease to oligometastatic disease. According to previous studies, the median time to maximum response after EGFR-TKIs was 2–2.7 months (1-3). Therefore, we have defined early LT as within 3 months before reaching maximal response to EGFR-TKIs, and late LT as longer than 3 months after reaching maximal response. To clarify this, we have made the following revision and added a reference as follows (see Page 5, lines 145 to 147, and References list number 31):

▪ **Changes in the text**

Page 5, lines 145 to 147

Based on previous studies that reported the maximal response to EGFR-TKIs occurring within 2–2.7 months, studies were classified into early LT (‘time to LT’ < 3 months) and late LT (‘time to LT’ ≥ 3 months) (29-31).

References list number 31

31. Al-Halabi H, Sayegh K, Digamurthy SR, et al. Pattern of failure analysis in metastatic EGFR-mutant lung cancer treated with tyrosine kinase inhibitors to identify candidates for consolidation stereotactic body radiation therapy. J Thorac Oncol. 2015;10:1601-7.

References

1. Lung Cancer. 2020;140:65-70.
2. J Thorac Oncol. 2015;10:1601-1607.
3. Int J Radiation Oncol Biol Phys. 2020;107:62-71.

▪ **Comment 4**

In the discussion, I think it should be highlighted that the LAT is indeed very heterogenous. Even if the lesions are treated with radiation, they varied widely in dose and fractionation. Some use SBRT techniques with large fractional dose in a few fractions but some used lower dose and higher fractions. Besides, not all metastatic lesions were irradiated/ ablated, and whether it gave similar results remained uncertain.

▪ **Reply 4**

We agree with the heterogeneity among the included studies. Specifically, there were differences in the modalities of LT between and within individual studies. Moreover, the heterogeneity arising from factors such as not all metastatic lesions undergoing LT, and variations in the locations of these lesions, necessitates caution in interpreting the results. We attempted subgroup analyses to overcome this heterogeneity but encountered difficulties obtaining individual data from each study, thus preventing us from conducting various subgroup investigations. We acknowledge these limitations in this meta-analysis, and we have added them to the discussion section as follows (see Page 7, lines 260 to 262):

▪ **Changes in the text**

Page 7, lines 260 to 262
Third, given that meta-analysis is based on the results of published articles and entails integrating various clinical details, such as LT modalities and types of EGFR-TKIs, a certain degree of heterogeneity is inevitable.

▪ **Comment 5**
I would also suggest the authors to elaborate a bit more on the merits of delayed RT, apart from a small volume of disease to perform LAT, it potentially rendered polymetastatic disease to oligometastatic disease, and the potential difference in the biology of polymetastatic versus oligometastatic diseases.

▪ **Reply 5**
We agree with your perspective on the benefits of delayed LT. Targeted systemic therapy, such as EGFR-TKI administration, not only reduces tumor burden but also has the potential to transform polymetastatic disease into an oligometastatic state, thereby impacting prognosis (1). Moreover, LT for residual resistance clones of high heterogeneity can induce a fundamental change in biological behavior, potentially delaying progression. (2) As per your suggestion, we have further elaborated on the merits of delayed LT in the discussion section and added references for clarity as follows (see Pages 6 to 7, lines 246 to 248, and Reference lists numbers 53 to 54):

▪ **Changes in the text**
Pages 6 to 7, lines 246 to 248
Additionally, EGFR-TKI treatment has the potential to transform PM into an OM state, which can impact prognosis (53). Furthermore, LT for residual resistance clones of high heterogeneity can induce a fundamental change in biological behavior, potentially delaying progression (54).
Reference lists numbers 53 to 54

53. Petrelli F, Ghidini A, Ghidini MA, et al. Better survival of patients with oligo- compared with polymetastatic cancers: a systematic review and meta-analysis of 173 studies. F1000Res. 2021;10:423.

54. Hu X, Li H, Liu H, et al. Assessing efficacy and safety of stereotactic body radiation therapy for oligometastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) wild type. Transl Cancer Res. 2021;10:184-94.

References
1. F1000Res. 2021;423.
2. Transl Cancer Res. 2021:10:184-94.

▪ **Comment 6**
Apart from that, it should be cautioned that the OS analysis can also be affected by the prevalence of T790M and the accessibility of osimertinib in different arms/ studies.

▪ **Reply 6**
Thank you for pointing this out. We agree with your opinion that the expression of T790M and the subsequent use of osimertinib can impact OS (1). We attempted subgroup analyses to assess the impact of these factors on the outcome. Unfortunately, only three studies (Chan et al., Deng et al., and Peng et al.) reported the prevalence of T790M after progression between groups. Among them, only Peng et al. reported the OS between groups. While there was no difference in the prevalence of T790M between the LT and TKI groups, a difference in OS was observed. However, caution is still warranted when interpreting the OS results. These limitations have been addressed in the discussion section as follows (see Page 7, lines 262 to 265):

▪ **Changes in the text**
Page 7, lines 262 to 265
Fourth, evaluating treatment outcomes in patients with advanced NSCLC largely depends on factors such as the overall response rate, the prevalence of T790M mutation, the presence of unfavorable prognostic factors, and the type of EGFR-TKI. However, this information was not available.

References
1. Transl Lung Cancer Res. 2023;12:742-53.

▪ **Comment 7**
Finally, there are no comparison between pre-emptive LAT and LAT upon progression on the efficacy, cost effectiveness and toxicity etc. It definitely deserves more attention and prospective studies, but it can be very difficult to conduct and accrue good number of patients.

▪ **Reply 7**
We agree with your observation and recognize the importance of evaluating the differences in efficacy, cost-effectiveness, and toxicity between preemptive LT and LT upon progression. Although we intended to conduct a meta-analysis to explore this issue, the limited number of studies meeting our criteria posed a challenge. There is undoubtedly a need for more prospective research in this field, and we look forward to the results of an ongoing study (NCT 02759835).

Reviewer C

▪ **Comment 1**
In addition, although the authors mention three RCTs, Ref. 36 is a single-arm trial, and the comparison group is the patients who dropped out of the screening, not a randomized trial. Also, the study accrual was terminated because the planned number of patients was not accumulated.
Reference 43 is an RCT, but again, the planned number of patients was not enrolled due to poor case enrollment.
To summarize without mentioning these details may mislead the reader. The details of the cited references need to be reviewed again and resubmitted.

▪ **Reply 1**
Thank you for bringing this point to our attention. In the process of re-evaluating the included studies, we discovered our mistake. The study by Chan et al. was not a RCT but a phase II single-arm prospective study. The comparison group consisted of subjects who failed screening with four or more metabolically avid residuals (defined as maximum SUV >2.5) on the PET-CT scan. Moreover, neither Chan et al. nor Peng et al. reached the planned number of patients due to slow accrual. Consequently, we have revised the related content as follows (see Page 5, lines 161 to 163, Page 7, lines 258 to 260, the fourth row of the second column in Table 1, and supplementary figure S1):

▪ **Changes in the text**
Page 5, lines 161 to 163
Among the 11 final studies, which covered 1,313 patients, two were RCTs (n = 194) (44,45), one was a phase II single-arm prospective study (n = 59) (37), and eight were retrospective case-control studies (n = 1,060) (35,36,38-43).
Page 7, lines 258 to 260
Second, although RCTs are considered the gold standard for evaluating intervention efficacy, this study had access to only two RCTs. Between these, the study by Peng et al. did not reach the planned number of patients (44).

▪ **Comment 2**
Nine of the 11 cited cases were reported from China. What is the status of local treatment for residual lesions as a general clinical practice in China? I wonder whether this is a strategy reserved for EGFR lung cancer or a treatment strategy for lung cancer in general.

▪ **Reply 2**
Thank you for your comment. According to the national lung cancer guidelines in China, this strategy is not exclusive to EGFR-mutated lung cancer but is a general strategy for all types of lung cancer. The modalities

of LT are diverse and not limited to surgery or radiotherapy. They include various techniques such as bronchoscope-mediated laser, high-frequency electrotome, radiofrequency ablation, argon plasma coagulation, microwave, laser, photodynamic therapy, cryotherapy, and others (1). We acknowledge that the study subjects included in this meta-analysis were biased in terms of ethnicity. Considering that the prevalence of EGFR mutation is higher among East Asians, 10 of the studies were primarily conducted on East Asian populations. Recognizing this limitation, we underscore the need for a well-designed prospective study that includes a diverse range of ethnicities to verify our results more accurately.

References
1. Chin J Cancer Res. 2022;34:176-206.

▪ **Comment 3**
Finally, any information on ongoing prospective trials as a future direction should be added.

▪ **Reply 3**
Thank you for highlighting this point. The limited number of randomized trials included in this study, coupled with the small sample sizes, is an important consideration. Furthermore, the scarcity of studies involving 3rd generation EGFR-TKIs underscores the need for additional research. In this context, the outcomes of ongoing prospective trials using 3rd generation EGFR-TKIs (NCT03410043 and NCT05167851) are anticipated. If these studies are successfully completed, we will be able to approach lung cancer treatment with a more precise and in-depth understanding. Accordingly, the related content has been revised as follows (see Page 7, lines 268 to 270):

▪ **Changes in the text**
Page 7, lines 268 to 270
Therefore, future trials such as NCT03410043 and NCT05167851 will provide valuable information on the efficacy and safety of 3rd-generation EGFR-TKIs in combination with LT.

Reviewer D

▪ **Comment 1**
While studies (PMID: 35460474, PMID: 38090314) suggest no significant difference in PFS with second and third-generation TKIs, the data on OS may be influenced by the therapeutic agent's type (PMID: 33984681). Have you explored subcohorts based on the type of TKI?
Progression has been linked to poor prognosis markers, such as TP53, in second-line treatment (PMID: 35242623). Is there any available data in your study collection regarding TP53 co-mutational status?

▪ **Reply 1**
Thank you for your insightful comment. The observation that afatinib showed more benefit in OS than osimertinib in NSCLC without brain metastasis with L858R mutation suggests that the type of EGFR-TKI may influence survival outcomes. We also agree that TP53 co-mutation is associated with poor prognostic factors related to survival outcomes.
In this regard, we attempted a subgroup analysis based on the type of EGFR-TKI and the prevalence of TP53 co-mutation. However, we faced challenges in obtaining individual data from each study. Only three studies (Chan et al., Hsu et al., and Wang et al. 2021) reported no statistically significant difference in PFS according to the type of EGFR-TKI, and there were no reports regarding OS. Furthermore, data on survival outcomes related to the prevalence of TP53 co-mutations were not available. These limitations have been added to the discussion section as follows (see Page 7, lines 262 to 265):

▪ **Changes in the text**
Page 7, lines 262 to 265
Fourth, evaluating treatment outcomes in patients with advanced NSCLC largely depends on factors such as the overall response rate, the prevalence of T790M mutation, the presence of unfavorable prognostic factors, and the type of EGFR-TKI. However, this information was not available.

▪ **Comment 2**
Do you believe that assessing additional prognosis markers non-invasivley,ie. through liquid biopsy before implementing local therapy, could stratify patients who might benefit from additional local therapy?

▪ **Reply 2**
Thank you for the interesting question. The presence of EGFR mutations in ctDNA is considered a negative prognostic factor. Furthermore, the elimination of EGFR-mutated ctDNA following the administration EGFR-TKI is associated with improved PFS and OS (1). Given these points, non-invasively assessing additional prognostic markers through liquid biopsy before administering LT could be beneficial. It may help stratify patients who might benefit from additional LT.

References
1. J Thorac Oncol. 2021;16:1647-62.

▪ **Comment 3**
Implementing additional local therapy involves collaboration among various healthcare professionals and incurs additional costs from different methods (radiotherapy, sugery, ablation therapy). Is there any data available on healthcare cost analysis and the benefits of specific types of local therapies?

▪ **Reply 3**
Thank you for your comment and question. One previous study reported that additional LT is cost-effective compared to maintenance systemic therapy for patients with oligometastatic NCSLC who respond to first-line systemic therapy (1). Administering additional LT involves variable healthcare expenditures and utilization of medical resources, depending on the technique, such as radiotherapy, surgery, or ablation therapy. However, obtaining individual data from each study was not possible.

References
1. Radiother Oncol. 2018;129:257-63.