Peer Review File
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Reviewer A

Comment 1: Overall, this is an interesting and well-written overview. As suggested by the evidence, when SBRT is combined with TKIs there is a significant increased PFS and minimal toxicity. As well, there is a favorable T790M mutation ratio. Importantly, this cocktail facilitates drug permeability by disrupting the blood-brain barrier and also reduces EGRF-TKI resistance through the targeting of residual tumour cells. Indeed, further advances of third-generation TKIs enable greater selectivity toward EGFR with improved benefit and tolerance. However, decreased white blood cell count remains a concern, especially if bacterial infections occur. which may lead to the development of infectious diseases, especially bacterial infections. The authors have nicely summarized the literature.
My only suggestion is to delve further into the promise of fourth-generation compounds to overcome multiple resistance. Overall, nicely written review.
Reply 1: Thank you very much for your professional review work and strong support to our article. Based on your suggestion, we have supplemented the future perspective of fourth-generation EGFR-TKIs at the end of the text, and briefly described the main achievements as well as the latest clinical progress.
Changes in the text: (see page 14, line 447-451)

Reviewer B

This is a well-written narrative review on the use of SBRT for EGFR-mutated oligometastatic NSCLC. Minor comments are as follows:

Comment 1: Line 50 – can omit "mostly" since adenocarcinoma, squamous cell carcinoma and 'other' includes all histologies.
Reply 1: Thank you very much for your helpful comments. As your advised, we have removed "mostly" in the original text. And the modified text is "The most prevalent form of lung cancer, non-small cell lung cancer (NSCLC), consists of adenocarcinoma, squamous cell carcinoma, and other pathological forms."
Changes in the text: (see page 3, line 83)

Comment 2: Line 69 – would specify "in NSCLC"
Reply 2: Thank you very much for your helpful comments. As your comment, we have changed "The prevalence of epidermal growth factor receptor (EGFR) mutations ranges from between 5% and 10% in White patients" to "The prevalence of epidermal growth factor receptor (EGFR) mutations ranges from between 5% and 10% in White patients in NSCLC".

Changes in the text: (see page 4, line 103)

Comment 3: Line 77 – would omit “and others”
Reply 3: Thank you very much for your helpful comments. As your advised, we have removed “and others” in the original text. And the modified text is “Moreover, the ongoing development and enhancement of TKIs have led to the emergence of third-generation EGFR-TKIs, including osimertinib, almonertinib, vormetinib, which are more highly selective for EGFR-mutated cells and provide patients with advanced EGFR-mutated NSCLC improved efficacy and therapeutic window than older TKIs.”
Changes in the text: (see page 4, line 110)

Comment 4: Line 161 – would specify "randomized controlled” study
Reply 4: Thank you very much for your helpful advised. We have modified the original text to “Moreover, the randomized controlled study by Tsai et al. confirmed that SBRT is also suitable for oligoprogressive NSCLC, leading to more than a four-times increase in PFS compared with standard care.”
Changes in the text: (see page 7, line 196)

Comment 5: Line 181-182 is confusing and I am unsure what the authors are trying to say
Reply 5: We are very sorry for not being clear about the content of the article. And we have changed “This is achieved by the implementation of a five-point dose escalation strategy, which is afterward assessed for its safety and efficacy” to “This is achieved by the implementation of a five-point dose escalation strategy, starting at 10 Gy/fraction and increasing by 0.5 Gy/fraction every second to third day to 12 Gy/fraction, which is afterward assessed to be safe and effective”.
Changes in the text: (see page 7, line 215-218)

Comment 6: Line 216 – would omit “and other compounds”
Reply 6: Thank you very much for your helpful comments. We have modified our text to “In response to this challenge, novel third-generation TKIs, including osimertinib, almonertinib, vormetinib, have been developed to specifically target the T790M mutation”.
Changes in the text: (see page 8, line 255)

Comment 7: Line 352 – would change “The curative effect … enhanced” to “Overall survival … improved”
Reply 7: Thank you very much for your helpful comments. We have modified our text from “The curative effect was shown to be considerably enhanced in the consolidation therapy group, with no observed occurrence of grade 3 or above toxicity” to “Overall survival was shown to be considerably improved in the consolidation therapy group, with no observed occurrence of grade 3 or above toxicity”.
Changes in the text: (see page 12, line 395-396)
Overall this is well written. I have no major comments.

Reviewer C

In this narrative review the authors present the current evidence on the combination of stereotactic body radiotherapy with TKIs in EGFR-mutated NSCLC. Before publication, however, I would recommend to address the following issues.

Comment 1: Page 6, lines 174 - 178: When giving doses of SBRT regimens, please mention the prescription isodose. The other possibility is calculating EQD2 or BED and giving the respective alpha/beta-values.

Reply 1: Thank you very much your suggestions. We have re-reviewed the citations carefully. However, the prescription isodose were not mentioned in the cited literature and therefore could not be supplemented in the manuscript. However, in clinical practice, 95% isodose line is commonly used.

Changes in the text: (see page 7, line 209-213)

Comment 2: Please write a separate section on pulmonary toxicity, which summarizes the information from all the different studies. It would also be helpful to include a table. The information on side effects is now spread in the section Clinical trials on combination therapy. In this context it is also necessary to point out whether the TKI was administered concomitantly to SBRT or not. Perhaps the table should be divided in two groups, one with the concomitant SBRT/TKI and the other with TKI interruption during SBRT. Equally important in this context: Do the authors recommend SBRT plus Osimertinib (or other 3rd generation TKIs) combined or would they rather recommend an interruption of TKI treatment during radiotherapy? This is an important question for clinical practice so it should be discussed in the section on toxicity.

Reply 2: Thank you very much for your valuable suggestion. We consider your suggestion is extremely professional and necessary. Therefore, we have re-reviewed the experiments mentioned in the articles and searched relevant papers. In the section of TKIs combined with concurrent SBRT, there are obvious differences in the incidence of pneumonia between a clinical study with TKI interruption and another with TKI maintenance. However, the findings of a prospective randomized controlled trial discovered through a literature search revealed the opposite effect. Furthermore, in the other clinical trials, including TKIs combined with consolidate SBRT and third-generation TKIs combined with SBRT, some trials did not specify the timing of TKI administration, while the rest were TKIs maintenance. Because of the vast differences between these clinical studies, comparing their pneumonia incidence is difficult. As a result, we primarily discussed the association between the timing of TKI administration and the incidence of pneumonia when TKIs were combined with concurrent SBRT.(see page 12, line 362-370) The remaining information is supplied in the Limitations and Perspectives section. (see page 14, line 444-445)

Changes in the text: (see page 12, line 362-370) (see page 14, line 444-445)

Comment 3: Conclusion: Please shorten this section to 3-4 sentences maximum. Also mention your recommendation on whether TKIs should be administered concomitantly or not.
Reply 3: Thank you very much your suggestions. We have simplified the conclusion, deleted inessential descriptions in section of the mechanism of combination therapy. (see page 14, line 442-454) What's more, because of the limited, incomplete and contradictory experimental information, there is no clear guideline to recommend whether TKIs should be used concomitantly. Therefore, this part of the content have been organized in the limitations and prospects of the article.(see page 14, line 432)
Changes in the text: (see page 15, line 455-469) (see page 14, line 444-445)

Minor
Comment 4: Why use hashtags instead of numbers for denoting the subsections?
Reply 4: Thank you for your comment. We used hashtags to prevent formatting clutter that might occur due to software compatibility issues. The problem has now been corrected. **Changes in the text:** (see page 3, line 77)

Comment 5: page 3, line 84: What is meant by: (…)third-generation TKIs provide represent superior PFS outcomes…
Reply 5: Thank you for your comment. We have modified our text from "third-generation TKIs provide represent superior PFS outcomes" to "third-generation TKIs provide significant increased PFS".
Changes in the text: (see page 4, line 118)

Reviewer D

Good review; requires small revisions as follows:
1. Final sentence in conclusion does not accurately describe what is mentioned in the results section.
Reply: Thank you very much for your valuable suggestion. In our revised manuscript, more details have been supplemented in terms of the selection of oligometastatic site, the optimization of combination therapy, and subsequent second-line therapy.
Changes in the text: (see page 15, line 465-469)

2. 186 - BED 100 Gy required in OMD when concurrent systemic therapy is delivered? Maybe discuss need for isotoxic approach.
Reply: We sincerely appreciate the valuable recommendation. By re-reviewing the references, we have modified the original article to "Furthermore, the biologically equivalent dose (BED) was calculated using the assumption that tumour and normal tissue alpha/beta ratios were 10 Gy (BED10) and 3 Gy (BED3), respectively. A research has shown that when utilizing appropriate fractionation schedules in which the BED10$\geqslant$100 Gy and BED3 $\leqslant$210 Gy, local control exceeded 85% and the risk of treatment-related mortality was less than 1% (24)".

Changes in the text: (see page 7, line 222-227)

3. Line 304 - important to discuss in Wang study that in upfront setting; ablative doses were not delivered and yet had high local control.

Reply: Thank you very much for your professional suggestion. We have re-reviewed the Wang study for three reasons for not using an ablation dose. First, there is no robustevidence in the literature to date (especially when this trial was designed) that higher doses cause more robust tumor control in the oligometastatic setting. Second, EGFR-mutant cases repre sent unique biology for which targeted therapy is much more locally effective than chemotherapy for nonmutated cases. Third, a wide variety of nonablative (including palliative) doses has been used in prior trials of local therapy for oligometastatic NSCLC.

Therefore, we have supplemented at the end of the article discuss about SBRT radiation dose.

Changes in the text: (see page 14, line 440-442)