Peer review file

Article information: https://dx.doi.org/10.21037/jtd-21-957

Reviewer A

Comments:

Paper structure:

Title: adequately reflect the content of the paper.

Abstract: correct. It properly describes the study and summarizes properly the study conclusions.

Introduction: provides a complete state of the art on the topic.

Methods: The proposed method is adequate for the study aim.

Results, tables and figures: adequate to answer the proposed question.

Information provided by tables and figures complete the data.

Discussion and references: complete, appropriated and references updated.

Limitations of the study are briefly commented. Conclusions came from the results and answer the proposed question.

Reply: Thank you very much for your great comments.

Changes in the text: None.

Comment 1: Indicating the origin of the European / American vs Chinese studies does not make sense.

Reply 1: Thanks for your critical comments. We wanted to display the basic characteristics of included studies. However, no further analyses were performed on this topic. These characteristics would be deleted from Table 1.

Changes in the text:

In results section, paragraph 2: The origin of study was deleted from Table 1. The sentence "Five studies were conducted by Americans or Europeans, while the remaining 3 were conducted by Chinese" was deleted from "baseline characteristics and risk assessment".

Comment 2: The term "criterial" appear many time in the text and must be changed for "criteria".

Reply 2: Thanks for your critical comments and we will revise the spelling mistake through the whole manuscript.

Changes in the text: The words "criterial" were revised to "criteria" throughout the manuscript.

Comment 3: Add to abbreviations list, KPS, ECOG, NOS.

Reply 3: Thank you very much for your critical advices. The term "KPS" and "ECOG" would be added to abbreviation list. The term "NOS" was not defined in original article.

Changes in the text: The term "KPS" and the term "ECOG" were added to abbreviations list.

Reviewer B

Comment for authors:

Thanks in advance for presenting the outline of this meta-analysis regarding the survival effect of surgical therapy in oligometastasized NSCLC patients. The data presented add clinically relevant information on treatment strategies in the prespecified cohort. The analyses were performed with respect to manifold settings, and some of the supplemental material is of great importance.

However, in my humble opinion some major issues have to be addressed before further processing the article in JTD.

Reply: Thanks for your critical comments.

Changes in the text: None.

Comment 1: General: 1) The term ‘systematic therapy’ is quite uncommon in this context. Hence, it should be replaced by ‘systemic therapy’, especially in the heading of the original article. Moreover ‘target therapy’ should be switched to ‘targeted therapy’.

Reply 1: Thank you very much for your critical advices. We are sorry about the misuse about these two words, and the correction would be made in revised manuscript.

Changes in the text: The words “systematic therapy” and “target therapy” were revised to “systemic therapy” and “targeted therapy” through the full-text, figures and tables.

Comment 2: General: 2) Instead of the correct term ‘criteria’ the authors use ‘criterial’ throughout the manuscript. This should be changed.

Reply 2: Thanks for your critical comments again. Misspelling of the word would be revised in text.

Changes in the text: The word “criterial” was revised to “criteria” throughout the manuscript.

Comment 3: General: 3) Before publication, the language needs profound English editing, as of now, it is hard to follow the substance due to misleading and incorrect terms. I will not correct single terms, sentences and grammar in the present revision. However, if not corrected in the subsequent outline, the manuscript should not be published in this way.

Reply 3: Thank you very much for your critical comments. A further revision and language editing were performed by Wenhao Liu and Yuanyang Lai, who were acknowledged in the text.

Changes in the text: Spelling and grammar mistakes were revised. Sentences were reworded to avoiding ambiguity and misleading. Adding “We would like to thank Wenhao Liu and Yuanyang Lai for their polishing in our paper” in acknowledgement.

Comment 4: Following this, I will present a point by point review of the aspects that have to be clarified before further processing the article. Abstract: p.3, ll 40: Please change into ‘… to explore whether local aggressive therapy could improve outcome of

oligometastatic non-small cell lung cancer patients.', as we are not treating NSCLC but patients with NSCLC. This aspect needs to be checked up throughout the manuscript.

Reply 4: Thanks for your critical comment. The misuse of "treating NSCLC" was revised to "treating patients with NSCLC" throughout the text.

Changes in the text:

1. In abstract: The sentence "This study aims to perform a pooled analysis to explore whether local aggressive therapy could improve outcomes of oligometastatic non-small cell lung cancer" was reworded to "This study aims to perform a pooled analysis to explore whether local aggressive therapy could improve outcomes of oligometastatic patients with non-small cell lung cancer".

2. The same mistakes were also reworded throughout the manuscript.

Comment 5: Please check the term "synthesized" on p3 ll. 46. I'd rather use conflate/ merge/ added up to.

Reply 5: Thank you very much for your comments. The word "synthesized" was changed into "merged".

Changes in the text: The word "synthesized" was revised to "merged" throughout manuscript. The same mistakes were also reworded to "merged" on Figure legends.

Comment 6: p. 3 ll 49 // p. 7 ll 172 (results): In the methods section, statistical significance was defined as $p<0.05$. Here, a p-value of $p=0.09$ is depicted as marginal statistical difference. This aspect should be changed with respect to formal correctness

in the abstract as well as in the manuscript text.

Reply 6: Thank you very much for your critical comments again. A formal depiction of p-value was corrected in the text.

Changes in the text:

1. In abstract: The sentence "There was a trend that median overall survival declined with the increasing proportion of N2-3 positive patients in local aggressive therapy group, with marginal statistical difference (p=0.09, rr=0.98)" was reworded to "There was a trend that median overall survival declined with the increasing proportion of N2-3 positive patients in local aggressive therapy group, but with no statistical difference (p=0.09, rr=0.98)".

2. In results section: The sentence "However, there was a trend that median OS declined with the increasing proportion of N2-3 positive patients in LT group, with marginal statistical difference (p=0.09, rr=0.98) (Figure 2)" was reworded to "There was a trend that median OS declined with the increasing proportion of N2-3 positive patients in LT group, but with no statistical difference (p=0.09, rr=0.98) (Figure 2)".

Comment 7: Introduction: p. 4, ll 66: The term 'principal place' should be replaced by a more common term, e.g. "NSCLC is a leading cause of cancer-related deaths worldwide, …".

Reply 7: Thanks for your critical comments. The term "principal place" was reword in the text.

Changes in the text:

In introduction section: The sentence “Non-small cell lung cancer (NSCLC) takes the principal place of cancer-related deaths around world” was revised to “Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths around world”.

Comment 8: p. 4 ll 71 // p. 4 ll 91 (methods): Oligometastases have been addressed by the IASLC in the 8. Edition of TNM staging as aspects of M1a, M1b and M1c (c.f. Goldstraw, P., Chansky, K., Crowley, J., Rami-Porta, R., Asamura, H., Eberhardt, W. E. E., … Yokoi, K. (2016). The IASLC lung cancer staging project: Proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM Classification for lung cancer. Journal of Thoracic Oncology, 11(1), 39–51. https://doi.org/10.1016/j.jtho.2015.09.009). Here, even stage IV A was redefined by M1a or M1b situation and multiple metastases (M1c) are expressed by stage IV B. Please introduce this aspect and thoroughly present the definition of oligometastasis in the present context and manuscript, defined as ≤ 5 metastases, irrespective of the organs involved. This aspect is heavily discussed. From a clinical point of view, a patient with each a single metastasis of the CNS, adrenals, liver, and bone is not regularly addressed by a surgical treatment approach of the thorax. Hence, this definition is very crucial in the subsequent analysis and needs intensified discussion in the context of the presented therapeutic sequence, as already partly present in the discussion section of the manuscript. Here, exemplary (see Suppl. Figure 6 A, point 1.62), upfront local therapy (presented only by Wang et al., 2020) is of borderline significance (p=0.05), which is later on depicted in the discussion (p. 11 ll 270). I must question, whether this study promotes the message of the present meta-analysis.

Reply 8: Thanks for your critical comments. First, the 8th TNM classification of NSCLC divides stage IV NSCLC into M1a, M1b and M1c, which indicates thoracic metastases, single distant metastasis and multiple metastases, respectively. Therein, M1a, M1b and a subgroup of M1c NSCLC patients belong to oligometastatic NSCLC. Up to now, the definition of oligometastases is still on debate. A systematic review analyzed the criteria of oligometastatic NSCLC in publications until now, and no formal definition was established in most of published studies. The upper number of lesion ranges from 1 to 8 with no limitation on organs involved. Present study was designed to enroll patients owing 1-5 metastases regardless of orangs which was consistent with majority of randomized controlled trials conducted in recent years. The definition of oligometastases is decided by number of metastatic lesions and the number of metastatic organs. For metastatic lesions, more than 90% oligometastatic NSCLC patients were with 1 metastasis, and nearly 100% patients were with less than 5 metastases. In present meta-analysis, 6 studies enrolling 273 patients reported the number metastatic lesions, and approximately 70% were with single metastatic lesion. In the present study, proportion of single distant metastatic patient not impact the survival of studies included. Thus, single distant metastasis might be a specific state in oligometastases, which were most likely to be diminished by LT. For metastatic organs, 5 studies enrolled in this study showed the maximum organs actually involved. Four of these five studies enrolled patients with no more than 2 organs involved. A more conservative definition of oligometastases (single organ) was used if surgery was taken as component of local therapy. A pan-European consensus reported a proposal of 1-5

metastatic lesions in no more than 3 organs may be an appropriate definition for oligometastases. Second, the study presented by wang et al. was an interim analysis comparing upfront local therapy and systemic therapy. The effectiveness of upfront local therapy on oligometastatic NSCLC should be evaluated in the future.

Changes in the text:

1. In discussion section, paragraph 3 and 6: The 3rd and 6th paragraphs of original manuscript were deleted.

2. In discussion section: The 2nd paragraph was revised as "Up to now, the definition of oligometastases is still on debate. A systematic review analyzed the criteria of oligometastatic NSCLC in publications until now, and no formal definition was established in most of published studies. The upper number of lesion ranges from 1 to 8 with no limitation on organs involved. Present study was designed to enroll patients owing 1-5 metastases regardless of orangs which was consistent with majority of randomized controlled trials conducted in recent years. The definition of oligometastases is decided by number of metastatic lesions and the number of metastatic organs. For metastatic lesions, more than 90% oligometastatic NSCLC patients were with 1 metastasis, and nearly 100% patients were with less than 5 metastases. In present meta-analysis, 6 studies enrolling 273 patients reported the number metastatic lesions, and approximately 70% were with single metastatic lesion. Single distant metastasis was categorized as M1b, which was considered to have more favorable survival than multiple metastases, in the 8th edition of TNM (tumor, node, and metastasis) classification. However, in the present study, proportion of single

distant metastatic patient not impact the survival of studies included. Further subgroup analysis for patients with single metastasis between local therapy and systemic therapy could not be made for the lack of survival data in this subgroup. For metastatic organs, 5 studies enrolled in this study showed the maximum organs actually involved. Four of these five studies enrolled patients with no more than 2 organs involved. A more conservative definition of oligometastases (single organ) was used if surgery was taken as component of local therapy. A pan-European consensus reported a proposal of 1-5 metastatic lesions in no more than 3 organs may be an appropriate definition for oligometastases"; 3. In discussion section: The 8th paragraph of original manuscript was revised as: "The sequence of LT and ST intervention is another key point for treatment strategy of oligometastatic NSCLC patients. Systemic therapy first could diminish tumor lesion to the maximum extent or screen out disease resistant to ST for recruiting suitable patients for further LT to avoid unnecessary injury or adverse events. However, delayed LT intervention might miss the opportunity of curative intent tumor elimination. On the contrary, removing tumor lesions directly could reduce tumor burden immediately to set the scene of following systemic therapy. Nevertheless, it may lead to unsuitable selection of patients with diffused cancer which are not detected yet. From this study, LT after first-line ST might be more beneficial for survival. There were three studies implement consolidative LT after first-line systemic therapy resulted an HR of 0.45 (95%CI: 0.34-0.60) for OS compared to ST. It was also presented in the study conducted by Jones and colleagues that neo-adjuvant therapy resulting survival benefits for lung resected oligometastatic NSCLC patients. Only one study underwent

LT before systemic therapy with an HR of 0.68, and the upper interval was 1.00 (95%CI: 0.47-1.00). For its interim analysis nature, the survival advantage of upfront LT should be re-evaluated during the follow-up".

Comment 9: Methods: p. 4 ll 91: Please see above.

Reply 9: Thanks for your critical comments again. Please see reply of comment 8.

Changes in the text: Please see changes in the text of comment 8.

Comment 10: p. 4 ll 92 and p. 5 ll 104: Please introduce the abbreviations of LT (local aggressive treatment) and ST (systemic treatment), used throughout the manuscript. Please report on the use of subsequent or previous systemic therapy in the LT cohort. With exemplary respect to Gomez et al. 2019 JCO, the local therapeutic strategies were performed as a consolidative regimen after upfront systemic therapy. Hence, the cohort definition differs from the presented local therapeutic regimen presented right now as radiation therapy and surgery vs. chemotherapy, targeted therapy, immunotherapy, and best supportive care (BSC). Additionally, I must raise the question, if patients treated by BSC should by evaluated in comparison to intensified surgical or radio-therapeutical local treatment approaches.

Reply 10: Thanks for your critical comments. First, the treatment strategy and sequence were displayed in Figure 1, column "Intervention". More accurate definitions of "LT" and "ST" were stated in methods section to avoid misunderstanding. Second, the definition of systemic therapy was revised as "ST included chemotherapy, targeted

therapy, and immunotherapy". Patients treated by best support care are generally with unfavorable performance status to tolerate toxicity or complications of local therapy. Thus, we removed the best supportive care from systemic regimens. Besides, no study enrolled in present meta-analysis applied best supportive care as standard or initial treatment. Cofounder biases of baseline characteristics and therapeutic regimens might exist between these two groups, especially in 5 retrospectively cohort studies. However, subgroup analysis showed that local therapy could offer survival benefits no matter in retrospective cohort studies or randomized controlled trials. 3. Potential cofounder biases of baseline characteristics were discussed in discussion section and mentioned in limitation part.

Changes in the text:

1. In methods section, paragraph 4: definition of local therapy and systemic therapy were revised as "LT was defined as surgery, stereotatic body radiotherapy with >20Gy, beam radiotherapy with dose >45Gy combined with or without ST. ST included chemotherapy, targeted therapy, and immunotherapy".

2. In discussion section, paragraph 4: Adding "However, a further comparison of performance score and age could not be made between these two groups due to lack of individual patient data, while it might lead to substantial heterogeneity and cautiousness of conclusions" to indicate the potential biases existing.

Comment 11: p. 5 ll 97: Please do not use (1), (2), (3) a.s.o. as bullet characters, when literature references are presented in the same manner.

Reply 11: Thank you very much for your great advice. Bullet characters were reset in the text.

Changes in the text:

In methods section, paragraph 5: Bullet characters were revised from (1), (2) and (3) ... to (I), (II) and (III) … in study selection part of methods section.

Comment 12: p. 5 ll 99: Please change the term 'NSCLC oligometastases' into 'oligometastatic NSCLC patients'.

Reply 12: Thanks for your critical comment. The terms "NSCLC oligometastases" throughout the manuscript were reword. Meanwhile, other ambiguous or inaccurate terms like "NSCLC oligometastases" were also revised in the text.

Changes in the text: The terms "NSCLC oligometastases" were revised to "oligometastatic NSCLC patients" throughout the manuscript.

Comment 13: p. 6 ll 123: Please change into 'A. p-value below 0.05 was considered statistically significant'.

Reply 13: Thanks for your critical comments. The sentence "A p-value under 0.05 was considered as statistical difference" was reworded.

Changes in the text:

In methods section, paragraph 8: The sentence "A p-value under 0.05 was considered as statistical difference" was reworded to "A p-value below 0.05 was considered statistically significant".

Comment 14: Results: p. 7 ll 155: Please present data on median age and a p-value comparator between the two cohorts, as age is a relevant cofactor of treatment choice.

Reply 14: Data on median age of each study were presented in table 2, column 4. However, a p-value comparison of age between local aggressive lung therapy and systemic therapy cohorts could not be retrieved and merged from original research.

Changes in the text:

In discussion section, paragraph 4: The 4th paragraph of discussion was reworded to "Good performance score is important for patient selection. Van den Begin and colleagues constructed a tool to select oligometastatic NSCLC patients for LT, and KPS performance score took the leading position to predict survival (27). In the present, 6 studies proposed ECOG≤2 or KPS≥70 as eligibility. In addition, median ages of LT patients seemed slightly younger than ST ones (53-63 vs 58-70). Younger patients may own better general condition to tolerate toxicity of LT, and it might be one of the reason that better survival was achieved in LT group. However, a further comparison of performance score and age could not be made between these two groups due to lack of individual patient data, while it might lead to substantial heterogeneity and cautiousness of conclusions" to discuss potential limitation on baseline characteristics of age and performance status.

Comment 15: p. 7 ll 157: Please present comparative data on the N2-3 status in both cohorts (p-value). If possible, please additionally present data of Karnofsky index or

ECOG between the two cohorts, as this is discussed in the manuscripts discussion section. Moreover, thoracic surgery – except in case of emergency or to reduce side effects – is commonly not recommended by European treatment guidelines in N3 situation. Please comment on this and discuss this later on in the discussion section.

Reply 15: Thanks for your critical comments. 1. A comparative p-value of N2-3 status between LT and ST cohorts was added to manuscript; 2. Eligible KPS or ECOG status was added as a new column of Table 2 named "ECOG 0-1/ KPS≥80"; Three RCT studies did not report the number of patients in each performance status point, but were designed with balanced recruitment of baseline characteristics. Four retrospective studies presented more than 70% of patients owing ECOG 0-1 point or KPS≥80 points in LT group, but with no statistical difference compared with ST group (p=0.159). 3. Thoracic surgery is not recommended for patients with N3 situation. However, no detailed information of whether thoracic surgery was performed on N3 positive patients could be retrieved from original studies. For patients with N3 positive, stereotactic radiotherapy or beam radiation was recommended as local treatment option.

Changes in the text:

1. In results section, paragraph 3: adding "Four studies enrolling 253 patients presented performance status. Of these patients, 90 (72.6%) patients were with ECOG 0-1 point or KPS≥80 points in LT group, and corresponding number in ST group was 83 (64.3%) (p=0.159). There were 5 studies enrolling 225 patients reporting proportion of patients with N2-3 positive. Thirty-five (28.7%) and 61(59.2%) patients were N2-3 positive in LT and ST group (p<0.001), respectively." to the 3rd paragraph to present

comparative p-value of ECOG 0-1/ KPS≥80 and N2-3 positive status between 2 cohorts.

2. In Table 2: Adding a column named "ECOG 0-1/ KPS≥80" to present detailed number and proportion of patients with ECOG 0-1/ KPS≥80 points.

3. In results section, paragraph 3: Adding the sentence "Four studies enrolling 253 patients presented performance status. Of these patients, 90 (72.6%) patients were with ECOG 0-1 point or KPS≥80 points in LT group, and corresponding number in ST group was 83 (64.3%) (p=0.159)" to the 3rd paragraph.

4. In discussion section, paragraph 4: the 4th paragraph of discussion was reworded to "Good performance score is important for patient selection. Van den Begin and colleagues constructed a tool to select oligometastatic NSCLC patients for LT, and KPS performance score took the leading position to predict survival. In the present, 6 studies proposed ECOG≤2 or KPS≥70 as eligibility. Three RCT studies did not report the number of patients in each performance status point, but were designed with balanced recruitment of baseline characteristics. Four retrospective studies presented more than 70% of patients owing ECOG 0-1 point or KPS≥80 points in LT group, but with no statistical difference compared with ST group (p=0.159). In addition, median ages of LT patients seemed slightly younger than ST ones (53-63 vs 58-70). Younger patients may own better general condition to tolerate toxicity of LT, and it might be one of the reason that better survival was achieved in LT group." to discuss potential limitation on baseline characteristics of age and performance status.

5. In discussion section, paragraph 5: the 5th paragraph of discussion was reworded to "Surgery and radiotherapy are both suitable choice for oligometastatic NSCLC

patients. Previous study systematically reviewed LT for oligometastatic NSCLC regardless of surgery or radiotherapy, no significant difference of OS was found between these 2 approaches. In present study, both surgery and radiotherapy could obtain survival benefits compared with ST in subgroup analysis. However, a lower HR of 0.33 (95%CI: 0.22-0.48) on PFS was observed in studies including surgery as component of LT compared to 0.55 (95%CI: 0.36-0.83) of those without surgery. Therefore, surgery still took an important role in LT application for oligometastatic NSCLC patients under suitable selection. It was worth noting that several studies enrolling N3 positive patients included surgery as local therapy, but presented scarce information of whether surgery was performed on these patients. For patients with N3 positive status, radiotherapy for lung is recommended rather than surgery. Thus, the superiority comparison of surgery and radiotherapy for oligometastatic NSCLC should be explored by head-to-head study" to further discuss the selection of surgery and radiotherapy.

Comment 16: p. 7 ll 158: Here you present data on six studies with only a single distant lesion (M1b) which significantly differs from 'oligometastatic' patients with five metastases in five organs. In my humble opinion, these 331 patients are very relevant to be analyzed independently. However, these analyses are not presented in the Supplementary Figures. If possible, please provide HR-data with median overall survival (mOS) and progression-free survival (PFS) on surgical treatment of patients with M1b situation.

Reply 16: Thanks for your critical comments. In the 8th TNM classification of non-small cell lung cancer, single distant metastasis in single organ is classified into M1b stage, which shows better survival rate than multiple metastatic lesions regardless of involved organ. However, only the proportion of patients with M1b stage could be retrieved from studies include in present meta-analysis with no individual patient data. Furthermore, no survival curve of M1b patients reported in studies included in present meta-analysis, so that the relative HR of M1b patients in local therapy or systemic therapy could be retrieved by the software "digitizer". Thus, we could not provide HR-data with median overall survival or progression-free survival on subgroup of patients with M1b situation.

Changes in the text:

1. In discussion section: the 6th paragraph was deleted;

2. In discussion section, paragraph 2: the 2nd paragraph was reworded to "Up to now, the definition of oligometastases is still on debate. A systematic review analyzed the criteria of oligometastatic NSCLC in publications until now, and no formal definition was established in most of published studies. The upper number of lesion ranges from 1 to 8 with no limitation on organs involved. Present study was designed to enroll patients owing 1-5 metastases regardless of orangs which was consistent with majority of randomized controlled trials conducted in recent years. The definition of oligometastases is decided by number of metastatic lesions and the number of metastatic organs. For metastatic lesions, more than 90% oligometastatic NSCLC patients were with 1 metastasis, and nearly 100% patients were with less than 5

metastases. In present meta-analysis, 6 studies enrolling 273 patients reported the number metastatic lesions, and approximately 70% were with single metastatic lesion. Single distant metastasis was categorized as M1b, which was considered to have more favorable survival than multiple metastases, in the 8th edition of TNM (tumor, node, and metastasis) classification. However, in the present study, proportion of single distant metastatic patient not impact the survival of studies included. Further subgroup analysis for patients with single metastasis between local therapy and systemic therapy could not be made for the lack of survival data in this subgroup. For metastatic organs, 5 studies enrolled in this study showed the maximum organs actually involved. Four of these five studies enrolled patients with no more than 2 organs involved. A more conservative definition of oligometastases (single organ) was used if surgery was taken as component of local therapy. A pan-European consensus reported a proposal of 1-5 metastatic lesions in no more than 3 organs may be an appropriate definition for oligometastases" to further discuss the definition and survival of oligometastases, including M1b subgroup.

Comment 17: Discussion: General: Except for adverse events, confounders for beneficial survival in the LT cohort (i.e. extractable age, performance status, exact definition of oligometastasis, subsequent and previous systemic therapies) were not sufficiently taken into account. Please add data and discussion context with regard to these aspects. Please additionally discuss, that at the moment the cohorts compared contain a) Systemic treatment approach plus radiation therapy and/ or surgery of the

thorax (LT group) versus b) Systemic treatment approach or best supportive care. With respect to this and to prevent misinterpretation, the presented Kaplan Meier curves in figure 4 need additional information. Possibly, subordinate survival analyses with the aspects of age, performance status, only a singular distant metastasis and with/ without previous and/or subsequent systemic therapy might help to define the LT's associated survival benefit.

Reply 17: Thank you very much for your critical comments. 1. As it is said above, age, performance status, exact definition of oligometastasis, subsequent and previous systemic therapy were all associated with beneficial survival of local therapy. These confounders were all designed with balance in randomized controlled trials. However, no subgroup analysis could be retrieved from original report based on these characteristics; 2. For studies with retrospective nature, these confounders could not be merged due to the lack of individual patient data, and we could not calculate HR for a definite subgroup of patients with younger/elder age, lower/higher performance status, M1b/M1c metastasis(es) or different systemic regimens. Nonetheless, the confounding biases induced by these factors should be emphasized and fully discussed. 3. Six studies containing 331 patients reported number of patients with single distant lesion. There were 88 (54.0%) patients in LT group and 85 (50.6%) patients in ST group with single distant metastasis with no statistical difference between 2 groups (p=0.128).

Changes in the text:

1. In discussion section, paragraph 2: adding discussion about cofounding factor "single metastasis" as: "However, in the present study, proportion of single distant

metastatic patient not impact the survival of studies included. Further subgroup analysis for patients with single metastasis between local therapy and systemic therapy could not be made for the lack of survival data in this subgroup".

2. In discussion section, paragraph 4: the 4th paragraph was revised to "Good performance score is important for patient selection. Van den Begin and colleagues constructed a tool to select oligometastatic NSCLC patients for LT, and KPS performance score took the leading position to predict survival. In the present, 6 studies proposed ECOG≤2 or KPS≥70 as eligibility. Three RCT studies did not report the number of patients in each performance status point, but were designed with balanced recruitment of baseline characteristics. Four retrospective studies presented more than 70% of patients owing ECOG 0-1 point or KPS≥80 points in LT group, but with no statistical difference compared with ST group (p=0.159). In addition, median ages of LT patients seemed slightly younger than ST ones (53-63 vs 58-70). Younger patients may own better general condition to tolerate toxicity of LT, and it might be one of the reason that better survival was achieved in LT group." to further discuss cofounding factor "performance status".

3. In discussion section, paragraph 6: the 6th paragraph was revised to "The sequence of LT and ST intervention is another key point for treatment strategy of oligometastatic NSCLC patients. Systemic therapy first could diminish tumor lesion to the maximum extent or screen out disease resistant to ST for recruiting suitable patients for further LT to avoid unnecessary injury or adverse events. However, delayed LT intervention might miss the opportunity of curative intent tumor elimination. On the contrary, removing

tumor lesions directly could reduce tumor burden immediately to set the scene of following systemic therapy. Nevertheless, it may lead to unsuitable selection of patients with diffused cancer which are not detected yet. From this study, LT after first-line ST might be more beneficial for survival. There were three studies implement consolidative LT after first-line systemic therapy resulted an HR of 0.45 (95%CI: 0.34-0.60) for OS compared to ST. It was also presented in the study conducted by Jones and colleagues that neo-adjuvant therapy resulting survival benefits for lung resected oligometastatic NSCLC patients. Only one study underwent LT before systemic therapy with an HR of 0.68, and the upper interval was 1.00 (95%CI: 0.47-1.00). For its interim analysis nature, the survival advantage of upfront LT should be re-evaluated during the follow-up" to further discuss the impact of intervention sequence.

Comment 18: p. 10 ll 242: Please explain the clause 'due to the inclusion of RCS to some extent' in the context of the previous sentence.

Reply 18: Thanks for your critical comments. In present meta-analysis, the median ages of local aggressive therapy patients seemed slightly younger than systemic therapy ones (53-63 vs 58-70). For the lack of individual patient data, we could not calculate exact p-value of age between these two treatment cohorts. In randomized controlled trials, baseline characteristics like age, performance status were balanced at recruitment. In 4 retrospective studies, more than 70% of patients owing ECOG 0-1 point or KPS≥80 points in LT group, but with no statistical difference compared with ST group (p=0.159).

Changes in the text:

1. In discussion section paragraph 4: deleted the sentence “due to the inclusion of RCS to some extent”.

2. **In discussion section paragraph 4**: reworded the 4th paragraph to “Good performance score is important for patient selection. Van den Begin and colleagues constructed a tool to select oligometastatic NSCLC patients for LT, and KPS performance score took the leading position to predict survival (27). In the present, 6 studies proposed ECOG≤2 or KPS≥70 as eligibility. Three RCT studies did not report the number of patients in each performance status point, but were designed with balanced recruitment of baseline characteristics. Four retrospective studies presented more than 70% of patients owing ECOG 0-1 point or KPS≥80 points in LT group, but with no statistical difference compared with ST group (p=0.159). In addition, median ages of LT patients seemed slightly younger than ST ones (53-63 vs 58-70). Younger patients may own better general condition to tolerate toxicity of LT, and it might be one of the reason that better survival was achieved in LT group”.

Reviewer C

Comments to authors: The authors present a meta-analysis of 8 total studies (3 RCTs, 5 retrospective) with the aim of determining whether local aggressive therapy (LT) to the primary tumor (surgery or radiotherapy) was associated with improved survival compared to systemic therapy (ST) alone in patients with oligometastatic NSCLC. In total, 499 patients were included in the pooled analysis, Kaplan-Meier was used to

estimate progression-free (PFS) and overall survival (OS), and linear regression was used to determine the association between clinical characteristics and survival. They found that both PFS and OS were extended by approximately 7 months in the LT group, which lead the authors to conclude that local aggressive therapy may improve survival in patients with oligometastatic disease, particularly in patients with N0-1 disease. This study was able to consolidate the available literature on oligometastatic NSCLC and perform important analyses, but I believe there are substantial issues that need to be addressed prior to consideration for publication. They are as follows:

Reply: Thanks for your great comments.

Changes in the text: None.

Comment 1: "Systematic therapy" should be changed to "systemic therapy" here and throughout the entire manuscript.

Reply 1: Thanks for your critical comment. The term "systematic therapy" would be revised to "systemic therapy" throughout the manuscript.

Changes in the text: All terms "systematic therapy" were reworded to "systemic therapy" in revision.

Comment 2: "Local aggressive therapy" should be defined here, even just to say "surgery or radiotherapy" would be sufficient.

Reply 2: Thank you very much for your critical comments. The term "local aggressive therapy" would be defined in abstract.

Changes in the text: The term “local aggressive therapy” was defined as “surgery or radiotherapy” in abstract.

Comment 3: Oligometastasis should be defined.

Reply 3: Thanks for your critical comments. Oligometastases was defined as 1-5 metastases regardless of organs in abstract.

Changes in the text: In abstract: the methods part was revised to “Pubmed, Embase and Web of knowledge were searched, and eligible studies investigating local therapy for non-small cell lung cancer with 1-5 metastases regardless of organs were included. Linear regression between survival and clinical characteristics were conducted. Hazard ratios of survival and adverse effects were merged. Pooled survival curves were carried out”.

Comment 4: The incidence of oligometastasis should be mentioned to give the reader an idea of how common this entity is.

Reply 4: Thanks for your great comments. A reference was added to show the incidence of NSCLC with oligometastases.

Changes in the text: A reference reported incidence of oligometastases was added as:

5. Parikh RB, Cronin AM, Kozono DE, et al. Definitive primary therapy in patients presenting with oligometastatic non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2014;89:880-7.

Comment 5: A newly published retrospective study in Cancers by the MSK group, entitled “Management of Synchronous Extrathoracic Oligometastatic Non-Small Cell Lung Cancer” is a relevant study and could be referenced, either here or in the discussion. A similar finding of pathologic nodal disease being associated with worse survival was reported in this study as well.

Reply 5: Thanks for your critical comments. The study mentioned above showed a significant survival benefits for oligometastatic NSCLC with multiple disciplinary treatments, which would add important and valuable information for curative strategy of these patients. It is an important reference for the present manuscript and added to reference list.

Changes in the text: Adding the study as reference 25.

1. In discussion section, paragraph 3: To support the trend of decreasing survival in patients with lymphnodes involved receiving LT as follow: “Several studies excluding N2 positive oligometastatic NSCLC patients from lung resection treatment due to possible detrimental survival, Presence of mediastinal lymphnodes metastases indicated worse survival, and high proportion of N2 positive patients might result in a negative effect of lung resection on oligometastatic NSCLC patients.

2. In discussion section, paragraph 6: To support the survival benefits of systemic therapy before local therapy for oligometastatic NSCLC patients as follow: It was also presented in the study conducted by Jones and colleagues that neo-adjuvant therapy resulting survival benefits for lung resected oligometastatic NSCLC patients.

25. Jones GD, Lengel HB, Hsu M, et al. Management of Synchronous Extrathoracic

Oligometastatic Non-Small Cell Lung Cancer. Cancers (Basel) 2021;13.

Comment 6: A citation should be provided for the definition of oligometastasis in Line 91.

Reply 6: Thanks for your critical comments. The defi

Changes in the text: In methods section, paragraph 4: Present study was designed to enroll oligometastatic NSCLC as 1-5 metastatic lesions regardless of organs (9,10,14).

Comment 7: Progression free survival should be defined in Line 117, namely which criteria (e.g., RECIST) were used to assess progression.

Reply 7: Thanks for your critical comments. The progression-free survival was retrieved from report of original studies. Only 3 studies (Iyengar 2018, Xu 2019 and Gomez 2019) were enrolled into pooled progression-free survival analysis. These 3 studies all determined progression-free survival according to imaging changes on radiographic scan.

Changes in the text: In methods section, paragraph 6: The sentence "First author, year of publication, study type, sample size, eligible criteria, clinical characteristics of patients, treatment strategy, median overall survival time (OS), median progression-free survival time (PFS), hazard ratios (HR) and number of adverse events were retrieved" was reworded to "First author, year of publication, study type, sample size, eligible criteria, clinical characteristics of patients, treatment strategy, median overall survival time (mOS), median progression-free survival time (mPFS), hazard ratios (HR)

and number of adverse events were retrieved as original report of studies".

Comment 8: Are you able to provide a table with a side-by-side comparison of the clinical and pathologic characteristics in the overall LT versus ST groups?

Reply 8: Thanks for your critical comments. A supplementary table 3 about clinical thoracic characteristics in LT and ST groups were added.

Changes in the text:

1. In methods section, paragraph 4: comparison of lymph nodes status and single metastasis was added: "Thirty-five (28.7%) and 61(59.2%) patients were N2-3 positive in LT and ST group ($p<0.001$), respectively. Totally 6 studies containing 331 patients reported number of patients with single distant lesion. There were 88 (54.0%) patients in LT group and 85 (50.6%) patients in ST group with single distant metastasis ($p=0.128$)".

2. In supplementary materials: A supplementary table 3 about clinical thoracic stage in LT and ST groups were added.

Comment 9: Was information provided for primary tumor size? Or tumor characteristics such as lymphovascular invasion, visceral-pleural invasion, or spread of tumor through air spaces? These could be interesting factors to include in Table 2 and investigate their association with survival.

Reply 9: Thanks for your critical comments. Primary tumor characteristics has been reported as an important factor affecting survival for oligometastatic NSCLC. However,

no further information like lymph-vascular invasion, visceral-pleural invasion or other characteristics was provided in original studies. Only clinical TN stage was reported, and these characteristics were added as supplementary table 3 mentioned in comment 8.

Changes in the text: A supplementary table 3 was added to show clinical thoracic stage.

Comment 10: Are p-values able to be generated for the comparisons presented in Figure 4A and 4B?

Reply 10: Thanks for your critical comments. The survival curves in Figure 4 were estimated and plotted on the basis of points retrieved from Kaplan-Meier curve in original studies. It was not a truly survival curve generated by individual patient data. A p-value between these 2 groups cannot be calculated, and it was not accurate even if it could be figured out.

Changes in the text: None.

Comment 11: The subgroup analysis in Supplementary Figures 3-7 is very interesting and should be expanded upon significantly. In Supplementary Figure 4, is the "treatment without surgery" group comprised exclusively of radiotherapy patients? If so, this should be stated and highlighted in the figure. It appears that surgery has a more significant effect on PFS; can this be mentioned in the results and addressed in the discussion? Given that most these analyses achieved statistical significance, you may consider replacing Figure 5 with one or more of these figures.

Reply 11: Thank you very much for your critical comments. In supplementary figure 4, treatment without surgery did comprise exclusively of radiotherapy patients. Patients received local treatment including surgery as component did show more advantage on progression-free survival than radiotherapy alone. The effectiveness of surgery was more mentioned and addressed in discussion. Figure 5 was replaced by supplementary figure 4 in revision. Supplementary Figure 7 was changed to Figure 6.

Changes in the text:

1. Figures: Figure 5 was replaced by supplementary figure 4 in revision. Supplementary Figure 7 was changed to Figure 6.

2. In results section: cumulative survival and subgroup analysis, paragraph 4: "In subgroup analysis, studies were divide by study type (RCTs and RCS), intervention type (with surgery and without surgery), local treatment sites (LT for lung and LT for both lung and metastases), sequence of LT and ST (consolidative LT or upfront LT) and systematic regimens (chemotherapy only or with targeted therapy). LT obtained more favorable survival in all subgroups. No statistically different heterogeneity was found in all subgroup analysis (Supplementary Figure 3, 4, 5, 6, 7)" was reworded to "In subgroup analysis, patients underwent LT with or without surgery both showed benefits compared to those with ST on OS and PFS. Furthermore, patients receiving surgery as component of multi-modality therapy showed relatively lower HR in PFS compared to these without surgery (Figure 5). As to sequence of LT and ST, HRs of consolidative LT (systemic therapy followed by local therapy) were relatively lower than upfront LT (local therapy first) on both OS and PFS (Figure 6). Besides, studies were divide by

study type (RCTs and RCS), local treatment sites (LT for lung and LT for both lung and metastases) and systematic regimens (chemotherapy only or with targeted therapy). LT obtained more favorable survival in all subgroups (Supplementary Figure 3, 4, 5).

3. In discussion section, paragraph 6: this paragraph was revised to "Surgery and radiotherapy are both suitable choice for oligometastatic NSCLC. Previous study systematically reviewed LT for oligometastatic NSCLC regardless of surgery or radiotherapy, no significant difference of OS was found between these 2 approaches (24). In the present study, both surgery and radiotherapy could obtain benefits on survival compared with ST in subgroup analysis. However, a lower HR of 0.33 (95%CI: 0.22-0.48) on PFS was observed in studies including surgery as component of LT compared to those without surgery of 0.55 (95%CI: 0.36-0.83). Therefore, selection of LT approach might depend on the feasibility of elimination, but surgery still took an important role in LT application for oligometastatic NSCLC patients. The superiority comparison of surgery and radiotherapy should be explored by head-to-head study".

Comment 12: Is information available about how metastases were treated? If so, it would be interesting to provide the breakdown of surgery vs. radiotherapy for metastases, and investigate whether there were survival differences between these two.

Reply 12: Thanks for your critical comments. Treatment strategy of local therapy was displayed in Table 1, column "intervention" and "LT sites". Clinical information and survival data of surgery and radiotherapy could not be retrieved from original study separately. A comparison between these two groups could not be achieved.

Changes in the text: In discussion section, paragraph 5: the 5th paragraph was reworded as follow: "Surgery and radiotherapy are both suitable choice for oligometastatic NSCLC patients. Previous study systematically reviewed LT for oligometastatic NSCLC regardless of surgery or radiotherapy, no significant difference of OS was found between these 2 approaches (21). In present study, both surgery and radiotherapy could obtain survival benefits compared with ST in subgroup analysis. However, a lower HR of 0.33 (95%CI: 0.22-0.48) on PFS was observed in studies including surgery as component of LT compared to 0.55 (95%CI: 0.36-0.83) of those without surgery. Therefore, surgery still took an important role in LT application for oligometastatic NSCLC patients under suitable selection. It was worth noting that several studies enrolling N3 positive patients included surgery as local therapy, but presented scarce information of whether surgery was performed on these patients. For patients with N3 positive status, radiotherapy for lung is recommended rather than surgery. Besides, clinical information and survival data of surgery and radiotherapy could not be retrieved from original study separately. A comparison between these two groups could not be achieved. Thus, the superiority comparison of surgery and radiotherapy for oligometastatic NSCLC should be explored by head-to-head study".

Comment 13: Please provide clear definitions of "consolidative LT" and "upfront LT," either here or in the methods section.

Reply 13: Thanks for your critical comments. A further definition of "consolidative LT" and "upfront LT" were given in results section.

Changes in the text:

In results section, umulative survival and subgroup analysis, paragraph 4: "In subgroup analysis, studies were divide by study type (RCTs and RCS), intervention type (with surgery and without surgery), local treatment sites (LT for lung and LT for both lung and metastases), sequence of LT and ST (consolidative LT or upfront LT) and systematic regimens (chemotherapy only or with targeted therapy). LT obtained more favorable survival in all subgroups. No statistically different heterogeneity was found in all subgroup analysis (Supplementary Figure 3, 4, 5, 6, 7)" was reworded to "In subgroup analysis, patients underwent LT with or without surgery both showed benefits compared to those with ST on OS and PFS. Furthermore, patients receiving surgery as component of multi-modality therapy showed relatively lower HR in PFS compared to these without surgery (Figure 5). As to sequence of LT and ST, HRs of consolidative LT (systemic therapy followed by local therapy) were relatively lower than upfront LT (local therapy first) on both OS and PFS (Figure 6). Besides, studies were divide by study type (RCTs and RCS), local treatment sites (LT for lung and LT for both lung and metastases) and systematic regimens (chemotherapy only or with targeted therapy). LT obtained more favorable survival in all subgroups (Supplementary Figure 3, 4, 5).

Comment 14: I would argue that there is a clear consensus definition of oligmetastasis, as reported in the 2019 JTO paper by Dingemans and colleagues (line 212), of "≤5 extrathoracic metastatic lesions in ≤3 organs." If this definition is used, additional studies may be able to be included and strengthen the statistical conclusions.

Reply 14: Thank you very much for your critical comments. The consensus report (2019 JTO paper by Dingemans and colleagues) did propose definition of oligometastases as "1-5 extrathoracic metastatic lesions in no more than 3 organs". However, we included studies not only by definition of oligometastases, but also by intervention types. Local therapy was defined as surgery, stereotatic body radiotherapy with >20Gy, beam radiotherapy with dose >45Gy. Systemic therapy included chemotherapy, targeted therapy, and immunotherapy. Palliative radiotherapy was permitted in systematic cohort with intent to relief symptoms and dose lower than local aggressive therapy cohort. Studies meet the following criteria were included: (I) randomized controlled trials or cohort studies comparing the effectiveness of local aggressive thoracic therapy and systemic therapy for Oligometastatic NSCLC patients; (II) Hazard ratio of death or disease-progression could be retrieved; (III) Kaplan-Meier overall or progression-free survival curve was reported. The exclusion criteria were as follow: (I) small cell lung cancer; (II) study with less than 10 cases; (III) palliative RT in systematic group with no clear statement of dose and intent; (IV) unbalanced local treatment for metastases, such as a cohort of lung LT treated patients compared with a cohort of lung ST but metastases LT treated patients. After re-searching of database, no more study was eligible.

Changes in the text: None.

Comment 15: What were the most common surgery-related complications mentioned in Line 277?

Reply 15: Thanks for your critical comments. Detailed information about post-operative complications was not displayed in previous published study. In our single center experience, 88 stage IV NSCLC patients underwent pulmonary resection, and 8 patients had post-operative complications. Among these patients, one was with air-leakage, 1 with chylothorax, 1 with pulmonary atelectasis and respiratory failure，2 with respiratory failure，2 with broncho-pleural fistula and 1 with pulmonary embolism (died in 30 days after surgery).

Changes in the text: None.

Comment 16: Overall, this is a relevant and important study with potentially valuable information contained within the primary and subgroup analyses. However, the substantial heterogeneity between studies included in this meta-analysis is given cursory mention in the limitations section. If this issue is not able to be resolved, every attempt should be made to address and investigate the differences between these two groups, that may have contributed to the survival differences reported. The conclusions listed (adverse effects, N2-3 patients) did not achieve statistical significance, in contrast to the subgroup analyses in Supplementary Figures 3-7. As a result, the true conclusions of this study should be reconsidered. Thank you for the opportunity to review this work.

Reply 16: Thank you very much for your critical comments.

Changes in the text:

1. In discussion, paragraph 8: the limitations paragraph was reworded as follow: “This study also has several limitations. Primarily, the study enrolled not only

randomized controlled trials, but also retrospective cohort studies, for the scarcity of publications. Inherent biases existed in these retrospective studies, like unbalanced patients baseline characteristics between local therapy and systemic therapy groups. There were more N2-3 positive in systemic therapy cohort and more probable younger patients in local therapy cohort. More randomized controlled trials should be conducted and data of this meta-analysis should be updated in the future. Besides, due to the heterogeneity of stage IV NSCLC, such as patients with different metastatic sites, the results of pooled analysis should be interpreted cautiously. Furthermore, for the lack of individual patient data and subgroup analysis in original report, further and detailed analysis could not be achieved. For instance, survival benefits of local therapy in N2-3 positive, single distant metastasis and surgically treated subgroup of patients. Last but not least, radiotherapy combined with immunotherapy also showed expecting effectiveness for oligometastatic NSCLC patients, but not included in present study due to its lack of survival data".

2. In discussion section, paragraph 9: the conclusion was reworded as follow: "In conclusion, local aggressive thoracic therapy could prolong 7 months overall and progression-free survival compared with systemic therapy in patients with oligometastatic non-small cell lung cancer. Consolidative local therapy might be associated with better survival compared with upfront local therapy. Benefits of local therapy for N2-3 positive patients should explore further".