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Reviewer A

In your institute, was there only one CPI patient without SBRT? If there were more patients, a comparison should be made between the SBRT group and non-SBRT group.

Reply:

Thank you very much for your reminding. As you could see in Figure 1, there was only one patient without complete SBRT indeed, since the selection of patients was performed in our Department of Radiation Oncology, information for patients without radiotherapy was not available at present. We totally agree with you that a comparison if there's enough data, will give a more comprehensive understanding of potential benefits of SBRT.

Changes in the text:

We have added this limitation in our discussion as reminded (see Page 19, Line 326-328).

・In your institute, the CPI patients with oligoprogression are mainly classified into two groups; monotherapy and combination therapy. The combination group patients might receive various cytotoxic drugs (such as pemetrexed, paclitaxel, and so on) or a molecular targeted drug. Do you think this fact influenced the PFS and OS? In addition, I don't think multivariate analysis is meaningful in this case because of the sample size.

Reply:

Sure, the combination of various drugs might influence the survival. We did further comparison as you suggested between monotherapy and combination therapy, as well as different combination strategy. No difference was found between mono and combination groups in survival both before and after oligoprogression (Table S3&S4). As for different combination strategies, before oligoprogression, we compared the three groups of chemo (12 patients)/ anti-angiogenics (5 patients)/chemo+ anti-angiogenics (3 patients) combination strategies and revealed no difference in PFS (P=0.180) and OS (P=0.627). After oligoprogression, 1, 3 and 13 patients received chemo/chemo+ anti-angiogenics / anti-angiogenics combination therapy respectively. We didn't observe difference of PFS-PO (P=0.564) and OS-PO (P=0.334) between chemo and anti-angiogenics combination therapy either. This might reflect the consistent benefits of adding SBRT. While since there might be bias with the small size of patients in chemo and anti-giogenics group, we didn't not present the comparison in the manuscript. It still required more samples to validate this finding. In the meantime, as you advised, our sample size was not enough to perform multivariate analysis indeed, univariable analysis / log rank test was used and checked for all statistical analysis in our study.

Changes in the text:

We have added the description of treatment strategies and results of comparisons in Results-Patients Characteristics & Outcomes Analysis (see Page 12, Line 196-198 & 202-206 & 217-221), Discussion (Page 19, Line 326-328) and Table 1&S3&S4.

・All 24 patients details （in Figure 3） must be reported in the new Table; age, histology, drug details, driver mutation, the lesion of oligoprogressive disease, and so on.

Reply:

Thank you very much for your suggestion. The details were added in Supplementary Table S2.

Changes in the text:

See supplementary Table S2.

Reviewer B

Wang et al present a retrospective analysis about the efficacy of stereotactic radiotherapy combined with CPI in NSCLC with oligoprogression under immunotherapy. The subject is clinically relevant and the report generally well-written. I habe some minor points:

1. page 3, lines 82-85 "Despite the significant progress in advanced NSCLC checkpoint inhibitors (CPIs) therapy, the majority of patients receiving CPIs typically exhibit acquired resistance over the course of treatment, primarily due to oligoprogression diseases" -> this is not true for NSCLC (and the reference cited = nr. 3 refers to melanoma): Oligoprogression does not affect the majority of CPI-treated NSCLC patients, but rather occurs in about 15-20% of cases, there is at least one through analysis on that, which is included as Reference 20 in the manuscript (Rheinheimer et al, PMID 32340408).

Reply:

Thank you very much for your reminding. We've replaced the reference to 3 summaries in lung cancer. During literature review, we could see that, oligoprogression-affected cases could be as low as 13% (Rheinheimer et al, PMID 32340408). At the same time, the current proportion of oligoprogression might also vary across treatment regimens (mono or combination, different antibodies, etc.), progression pattern (acquired resistance, or a sample description of 'progression', etc.), or definition of oligoprogression (number of sites, including CNS or not, etc.), and even different treatment centers. Therefore, we gave a range of patients with oligoprogression at 13%-56% as reported by the three through studies.

Changes in the text:

We have rephased the description and ratio of oligoprogression in Introduction Section. (see Page 6, Line 85-86).

2. Figure 1 flowchart: if the total number of diagnosed NSCLC patients in the same period is available, it should be added at the highest level of the figure (is the total/overarching number of NSCLC patients, of which a subset was treated in the Radiotherapy center etc). If this is not available, for example because patients are diagnosed externally and only a subset is referred to the Radiotherapy Center for treatment, then the text in the upper-most box of the figure should be modified to "patients treated with stage III-IV..." instead of "patients diagnosed with stage III-IV..."

Reply:

Thanks, that's a very important point. The fact is just like you've mentioned, our patients are diagnosed externally and only a subset is referred to the Radiotherapy Center for treatment, we've modified the text in the upper-most box of the Figure 1 to "patients treated with stage III-IV" as you suggested.

Changes in the text:

See Figure 1 and the description in Results-Patient on Page 12, Line 181.

3. page 3 line 123-124: "oligoprogression (defined as a condition characterized by a progression in a maximum of 2 metastatic sites", but in the Figure 1 oligoprogression is defined as "progression in a maximum three metastatic sites" (third box on the left side) -> please clarify and present in a uniform manned (two vs. three as the dut-off in the definition of OPD in this study).

Reply:

Thanks a lot and sorry for the confusion caused. Our definition of OPD is "a maximum of 2 metastatic sites" as indicated in Methods-Inclusion criteria. We've made correction in Figure 1.

Changes in the text:

See updated Figure 1.

4. page 4 lone 127 "patients with systemic progression or who received systemic therapy other than immune CPIs prior to the development of oligo-progressive disease were excluded" -> since this study included also patients with second/third-line immunotherapy (Table 2), it would be more accurate to rephrase this as "patients with systemic progression or who received systemic therapy other than immune CPIs during the development of oligo-progressive disease were excluded".

Reply:
Thank you very much for your straightforward suggestion, we've updated the description as suggested.
Changes in the text:
See Page 8, Line 126-128.
5. page 4 line 158-160, definition of PFS-PO: "Post-oligoprogression progression-free survival (PFS-PO) was defined as the time between the date of treatment of oligoprogression and the date of subsequent radiologic progression" -> "or death"
Changes in the text:
See updates on Page 10, Line 163.
6. page 5 line 199: in 29% (7/24) of cases the systemic therapy was escalated after SBRT -> could the authors provide the efficacy parameters also for the subset of patients (17/24) who continued the same systemic treatment after SBRT? It would be nice to demonstrate that this was comparable to the outcome of the entire group of 24 patients, because in the 7/24 patients who received modified treatment, the addition of cytotoxics or anti-angiogenics could confound the parameters of SBRT efficacy.
Reply:
Thank you very much for pointing out this potential influence. We listed regimens of each patient in Supplementary Table S2 and compared the PFS-PO and OS-PO between those 7 patients with modified strategy and 17 patients with consistent strategy before oligoprogression. As shown in Table S3&S4, no difference was found between this two group (mPFS-PO, 16 months (modified) vs. 11 months (consistent), P=0.979; mOS-PO, 34 months (modified) vs. 22 months (consistent), P=0.663). Although longer survival was observed among modified group, it did not reach a significant level. A larger sample size is needed to draw more solid conclusion.
Changes in the text:
We have added description in Results-Outcome Analysis (Page 13, Line 202-206 & 218-221), Discussion (Page 17, Line 281-285) and Table S3&S4.
7. page 6 line 221-224: if possible, the authors could provide all AE as a supplementary table (optional).
Reply and changes in the text:
Thanks for your suggestion, we have listed AEs in Table 3.
8. page 6 line 259: PD-L1 positivity is not only associated with benefit from TBP, but also with the occurence of oligoprogression itself (Ref. 20, Rheinheimer et al), which suggests that immunologic tumor control is an important prerequisite for both phenomena.
Reply:
Yes, Rheinheimer et al. has presented a comprehensive description of patterns of OPD and found that, OPD was associated with higher tumor PD-L1 expression ($p < 0.001$). With the increasing adoption of CPIs, OPD is becoming a common and important issue for those with higher PD-L1 expression. Hope discussions on overcoming strategies will give a comprehensive understanding and solutions suggestions for this group of patients.
Changes in the text:
See Discussion section on Page 16-17, Line 273-277.

Reviewer C

This is a retrospective case series that describes the outcomes in a cohort of 24 patients.
I think the question of overcoming resistance to immunotherapy is important and the addition of SBRT after oligometastatic progression is a reasonable starting point. However, given that this is a case series I think we need to be upfront about the limitations of the study and the ability to draw any strong conclusions.

I think the key message of this study is that it shows that this is a feasible and safe treatment option with reasonable PFS in this cohort of patients.

I am not sure it is valid to compare PFS to PFS-PO in the same patient cohort and claim that there is a benefit – as this inherently has bias. It may be better to look at rates of PFS in similar patients who did not have Subsequent SBRT? Possibly compare to rates described in the literature or registry data.

Reply:

Thank you for your valuable suggestion. We totally agree that a comparison between PFS-PO and PFS was not valid to drive a conclusion of "benefit". We rephrased our description and clarified that our PFS of 10 months was within the range of previous summaries of treatment before olioprogression, which indicated that baseline of our patients was comparable to other studies. And then, we compared the results of our 24 patients to reported PFS-PO and OS-PO, to illustrate its potential benefits of combing SBRT to the ongoing CPIs. There are reports on OS after acquired resistance (no distinction of oligoprogression or systemic progression, or treatment strategies after progression)(reference 3), OS of treatment beyond progression by CPIs (no distinction between oligoprogression and systemic progression, combing strategies after progression) (reference 18&21), PFS and OS of combing radiotherapy to immunotherapy after oligoprogression (included patients with SD response to previous CPIs, not sure what kind of radiotherapy is) (reference 6) and PFS and OS treated by SBRT on one of lesions among patients with at least 2 sites of metastasis after resistance to CPIs (reference 22). Therefore, we indirectly compare our results to published results, and it's better to perform, as you suggested, a simultaneous comparison with those developed olioprogression and adopted strategies other than SBRT. We mentioned this limitation in Discussion section.

Changes in the text:

We have modified the text in Discussion on Page 15-16, Line 246-247 & 252-259 & 266-268.

More descriptive clinical details would help add to the message of this study. I think it is important to be very specific with the immunotherapy regimens used. Please mention immunotherapy used (no mention of each drug). Additionally, It is also unclear whether those patients that had detected with mutations were treated with targeted therapy prior. If not, it might be worthwhile clarifying why not.

Reply:

Thanks for your reminding. A detailed description of regimens and clinical information is listed in supplementary Table S2. Among all patients, three were EGFR mutant (2 had insertion on exon 20, 1 had SNV on exon 20) and they all received CPIs as 1st line treatment. Patient 1 and 13 had EGFR 20ins which showed limited response of EGFR-TKIs, plus they had a higher PD-L1 expression at 35% and 10%, the patient then decided to adopt CPIs at first line. Patient 2 had a SNV of p.D770E which was barely reported and had a negative PD-L1 expression, while considering its LIPI at 1, the patient decided to try CPIs combined with chemotherapy. It turned out the three patients all showed objective response and achieved PFS longer than 9 months.

Changes in the text:

We have added the clarifying with supplementary Table S2.

The results mention that 7 patients received concurrent chemotherapy and anti-angiogenesis treatment as well post SBRT (line 200-201)– Please clarify the details of this cohort. Should this patient cohort be excluded as additional treatment will bias treatment outcomes?

Reply:

Sure, we gave the detailed regimens in Table S2 and did further analysis on your suggestions (Table S3&S4). There're 7 patients who received additional chemotherapy o anti-angiogenesis after oligoprogression. While, no difference was found between those and patients who continued the same strategy (combination therapy or maintenance monotherapy). We also looked at the impact of mono or combination therapy after oligoprogression, and no difference of survival was discovered either. Therefore, we summarized that treatment strategy (mono or combination, strategy modified or not) might bring no impact on survival, while the sample size might not be able to draw solid conclusions.

Changes in the text:

Comparisons were presented in Results (Page 13, Line 218-221) and Discussion (Page 17, Line 281-285).

More detail regarding adverse outcomes would be important – perhaps incorporate a table of

adverse events – including radiation related and immunotherapy related.

Reply:

Thanks for your suggestion, we have listed AEs in Table 3.

In the discussion it would be important to comment on the authors thoughts of presumed mechanism that leads to this apparent synergism between immunotherapy and SBRT and what this implies for future treatment paradigms in NSCLC.

Reply and changes in the text:

Thank you for sharing this enlightening advice. An exploration of potential synergism and future treatment paradigms is of great value for patients. We have added our discussion on Page 17-18, Line 292-307 & 315-319.