Peer Review File

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REVIEWER A

Comment 1: *"Subset analysis of patients with synchronous oligomet. disease receiving SBRT to the oligometastatic leasion vs. SBRT for locally recurrent or metachronous lung mets should be performed."*

Reply 1: Addition of figure 1b) and 1c) which show LPFS KM curves and log rank test of synchronous and metachronous subsets. Figures 2b) and 2c) show this same information but with OS. We added figure 3 b) showing cumulative incidence curve of local failure with death as a competing risk factor for total sample and for synchronous subset. Table 3 showing subdistribution hazard ratios of local failure with death as a competing risk for total sample, synchronous subset and metachronous subset. Tables 3, 4, and 5 show patient and lesion-based univariate and multivariate cox regression analysis for synchronous versus metachronous disease. Figure 4b) and c) shows patient-based (instead of lesion-based) OS KM curves and log rank test of synchronous and metachronous subsets.

Comment 2: *"Baseline characteristics should be briefly mentioned in results and discussion."*

Reply 2: Phrases detailing age, gender, and prior treatment added to beginning of Results section L161.

Comment 3: *"L185ff: "We also examined" sounds like an exploratory endpoint, however this paragraph refers to the main endpoint. Phrasing should be changed."*

Reply 3: L194 changed from "we also examined" to "The primary aim of our study was to investigate"

Comment 4: *"L216ff: The finding of better local control in the case of adeno carcinoma also is in line with clinical experience (in general: SC: poor local control, early mediastinal lymph node involvement, relatively late distant mets. AC: good local control, late mediastinal lymph node involvement, relatively early distant mets.) A phrase should be added referring to the clinical experience."*

Reply 4: Phrase referencing clinical experience added at line 222: "Our findings dovetail with the existing clinical evidence that pulmonary SqCC is associated with worse local control compared to pulmonary adenocarcinoma, regardless of stage at diagnosis." Corresponding reference also added

REVIEWER B:

Comment 5: *"First is a lack of data on systemic therapies. While the authors mention concurrent chemotherapy (i.e., delivered with SBRT), systemic therapy details are critical to interpreting these data, especially with shifting standards-of-care in NSCLC during the study period. For example, if there were patients with PD-L1 > 50% on pembrolizumab monotherapy or patients with EGFR-mutated NSCLC on Osimertinib (much more common among adenocarcinoma histology), SBRT is certainly not the only therapy impacting LPFS. The authors should also present data on how many patients were on systemic therapies before SBRT and how many were on systemic therapy after."*

Reply 5: In the sample characteristics in table 1, we added data referring to number of patients in each histologic subgroup who received pre-SBRT immunotherapy, pre-SBRT chemotherapy, post-SBRT

chemotherapy, and post-SBRT immunotherapy. In Tables 3, 4, and 5 we also performed univariate and multivariate cox regression analysis of pre and post chemo and immunotherapy.

Comment 6: *"Second, the authors performed this analysis at the level of single treated lesion. It would have been more effective to perform this analysis at the level of the patient, and subsequently reporting the number of lesions treated with SBRT (i.e., 1 vs. >1). By performing this analysis at the level of a single lesion, the authors make a big assumption that the disease biology of a single lesion is unique, even we're talking about multiple lesions within the same patient."*

Reply: We added proportions of patients with 1 SBRT-treated lesions and with >1 SBRT-treated lesions to the sample characteristics in Table 1. We also performed Kaplan Meier analysis of patient-based overall survival for the whole sample and for subsets of patients with synchronous and metachronous disease. We also added Figure 5 where we performed separate patient-based Kaplan-Meier analysis of 1 SBRT-treated lesion and >1 SBRT treated lesions subsets. We performed additional patient-specific univariate and multivariate analysis, tabulated in Table 5.

Comment 7: *"Third, and most importantly the degree to which other covariates impacted LPFS and OS is unclear. For example, there is not a complete univariate or multivariate regression model for these outcomes. Only disease histology is presented as a hazard ratio, which appears to be a univariate analysis. Each of the variables collected in Table 1 should have a P value (using paired t tests, chi-square, when appropriate). Then each variable should be analyzed using Cox hazard ratios to eventually build a multivariate model. It is very possible that tumor size and dose are confounding these results."*

Reply 7: We performed the appropriate tests (t-test, proportions test, chi square) on all the variables listed in Tables 1 and 2 and added columns listing each corresponding p-value. We added Tables 3, 4, and 5 which tabulate lesion and patient-based univariate analysis and multivariate analysis to assess impact of co-variates on histology.

Comment 8: *"Fourth, it's difficult to ascertain when these patients were being treated with SBRT, which is important to contextualize. I'd recommend including whether these patients had Synchronous vs. Metachronous oligometastatic disease, whether any had oligoresidual disease, whether all sites of oligometastasis were treated, etc."*

Reply 8: We added proportions of patients with synchronous disease and with metachronous disease to the sample characteristics in Table 1. We listed our definition of synchronous and metachronous in Materials and Methods, L143 (Synchronous lesions=appearing within 6 months of each other, metachronous=appearing at least 6 months before or after the other). We also added figure 1b) and 1c) which show LPFS KM curves and log rank test of synchronous and metachronous subsets. Figures 2b) and 2c) show this same information but with OS Addition of figure 3 b) showing cumulative incidence curve of local failure with death as a competing risk factor for total sample and for synchronous subset. Table 3 showing subdistribution hazard ratios of local failure with death as a competing risk for total sample, synchronous subset and metachronous subset. Tables 3, 4, and 5 show patient and lesion-based univariate and multivariate cox regression analysis for synchronous versus metachronous disease. Figure 4b) and c) shows patient-based (instead of lesion-based) OS KM curves and log rank test of synchronous and metachronous subsets.

Comment 9: *"In defining OMD, how are brain metastases and regional lymph node metastases counted?"*

Reply 9: We added a phrase to Materials and Methods, L99, specifying that we defined oligometastatic disease as fewer than five total metastases at distant sites including, but not limited to, contralateral lung, contralateral pulmonary lymph nodes, bones, and brain. We specified that we also included SBRT-treated regional pulmonary lymph nodes with recurrent disease after previously-treated early stage disease.

Comment 10: "*Treatments were delivered with once-weekly fractionation here, which, to my knowledge is not the most common method of delivering SBRT to patients with OMD. Many would deliver 5 fraction SBRT course daily or at most every other day. This should be elaborated upon in the discussion, as it likely effects the biologic effect of SBRT and the toxicity risk.*"

Response 10: Section added to discussion starting at L295 that acknowledges this unconventional fractionation schedule and addresses the need for future research to account for fractionation as another possible confounding variable that is responsible for our findings on histology

Comment 11: "*The authors present the Cox regression analysis death as a competing risk factor; it's unclear whether this was done in their KM analyses. How were patients censored in the Kaplan Meier analyses?*"

Response 11: Added two sentences in Materials and Methods, starting at L150, detailing which patients were censored in KM analyses: For LPFS KM analysis, patients who were alive and without local recurrence at the end of the study period were censored. For OS KM analysis, only patients who were alive at the end of the study period were censored.