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Reviewer A

Comment 1A. Please clarify the definition of upfront thoracic therapy. For the surgical group, what kind of procedures did patients receive (e.g., wedge resection, sublobar resection, lobectomy, the extent of mediastinal lymph node dissection)?

Comment 1A. A footnote in Table 1 now specifies: “thoracic resection included lobectomy and lymph node dissection (n=3) and sublobar resection (n=6); with lymph node dissection or sampling.”

Comment 1B. For the radiotherapy group, what dose/fractionation schedule did the patient receive? It is important to know if the thoracic therapy is either radical/ curative or palliative. The authors reported the BED ranged from 39-141Gy(alpha/ beta=10) in the radiotherapy group. However, a BED dose less than 60Gy(alpha/ beta=10), equivalent to 50 Gy/25 fractions, is not considered radical/curative in intent.

There is not a fine line between what would be conisderd curative and palliative dosing for NSCLC. Palliative dosing can results in long-term control. We now cite such studies and describe the heterogenous doses as a limitation.

We now explicitly state “Three patients received a BED of <60 Gy” on Page 10 of the results. In the discussion we state (on Page 18): “Of note, the vast majority of patients in our study were treated definitively, though 3 received a BED of <60 Gy; however palliative radiotherapy dosing of NSCLC has been associated with favorable control and survival outcomes in select patients.” And on Page 19 we added “There was heterogeneity in the treatment (surgery vs. radiation) and radiotherapy dosing of those undergoing UTT.”

Comment 2. For the TTP events (including overall, extracranial, intracranial, specific sites), the figures actually describe freedom from TPP. The authors are encouraged to use competing risk analysis to report the cumulative incidence of progression events instead.

Thank you. We have reworded the figures to say “Freedom from progression”

As the main focus of our work is to describe patterns of recurrence, with the survival outcomes being primarily descriptive and not expected to change appreciably with inclusion of competing risks, we opted to not perform these

additional analyses.

Comment 3. Please clarify whether the TN stage is based on clinical or pathological (for the surgical group) in the Materials and Methods.

Response: The foornote in Table 1 now states: "Staging was clinical in all but the 9 patients who underwent definitive resection."

Comment 4. ds-GPA should be diagnosis-specific formally instead of disease-specific.

Response: Thank you picking up on this. This was corrected.

Comment 5. The major concern of the research is the lack of molecular subtyping of NSCLC patients. Among the 92 patients with adenocarcinoma histology, less than half were assessed for molecular characteristics. This pitfall makes the research much less valuable in nowaday practice.

Response: We agree and acknowledge this in the discussion (Page 19) "Another limitation is that EGFR and ALK status was known in only 38 (41.3%) patients with adenocarcinoma histology, as the majority were treated before our institution routinely tested for these mutations." However, most patients do not have driver mutations and therefore these results still have utilty.

Comment 6. The dose range for WBRT is wide and not in concordance to the current guidelines.

Response: We agree, though most received typical WBRT doses. The results now state (Page 9): "All but 1 patient received ≤15 fractions and only 2 received <30 Gy; all others received 30 Gy in 10 fractions or 35-37.5 Gy in 14-15 fractions."

Comment 7A. In Table 1, the sum of patient numbers will not be 139 for histology and UTT.

Response: The histology should have been 32 under "other". This was a typographical error (the percentages were correct but the numbers were not). We corrected that error and appreciate the reviewer noticing this.

Comment 7A. It seems that only patients with synchronous brain metastases (n=88) are counted.

Response: UTT only reflects treatment of 'synchronous patients' since all 'metachronous patients' previously had their primary tumor addressed with

local therapy. We now specify this in a footnote, and appreciate the reviewer asking for clarification.

Comment 8. For the definition of UTT, it is described as "either thoracic surgery and/ or radiotherapy prior to any locoregional progression.". Is it means that it could be performed before, after, or at any time point in relation to brain metastases? I think there will be a substantial bias to calculate the TTP since patients did not receive UTT in a similar time window.

Response: We now state on Page 9-10: "For patients undergoing UTT, the range of time from initial diagnosis to completion of treatment of thoracic disease (prior to any evidence of progression) was broad (range 1-12 months); though for most, it was on the order of months (2nd-3rd interquartile range: 1.9-3.9 months)."

Comment 9. Please avoid the use the term "significant" or "significantly" for the interpretation of "p" value.

Response: We have edited the text as suggested

Comment 10. There will be a lot of biases when analyzing patients with heterogeneous characteristics retrospectively, especially the bias by indication of UTT. The inclusion of both synchronous and metachronous groups introduces even more biases. The authors should focus on a more uniform group to evaluate the benefit of UTT.

Response. We agree that any retrospective study will have inherent biases. We specifically separately analyses synchronous patients separately from metachronous patients in order to mitigate some biases.

Reviewer B

Comment 1. A very interesting research despite its retrospective nature. There is little literature on recurrence pathways in these patients.

Response: Thank you for the favorable comments

Some changes are suggested in different sections:

Comment 1. "Keywords": you could add "brain metastases"

Response: Thank you for this suggestion. This was corrected.

Comment 2. " Patient and treatment characteristics":
- Text references should be identified using numbers in round brackets.

Response: Thank you. This citation formatting was corrected. Thank you for pointing this out.

Comment 3. - You should add rates patients with chemotherapy vs molecular targeted therapy because it could modify patients prognosis. In text, you write "Eighty-five (62.0%) received upfront systemic therapy with first line chemotherapy (for at least 1 cycle) or a molecular targeted therapy". It is too general.

Response: The following text was added on Page 9: "Of these 8 patients, 4 received upfront tyrosine kinase inhibitor (TKI) targeted therapy, 2 received upfront chemotherapy and ultimately TKI therapy for salvage, and 2 were assessed for mutation status at the time of disease progression (as targeted drugs became standard of care) but were unable to receive systemic therapy due to declining performance status."

Comment 4A - Patient dosage and fractionation in SRS should be more explained. Were all patients (SRS alone or after surgery) performed in one fraction?

Response The text now explicitly states on page KK: "All SRS was delivered in 1 fraction." on Page 9 and we added "single-fraction" to the abstract and introduction.

Comment 4A –
"Analysis of progression among patients with synchronous brain metastases":
- Perhaps the confidence intervals of the HR should be stated in the main text.

As the data were analyzed by someone who has since left the University, we were unable to collect the confidence interval data, though the main message of this work is the patterns of recurrence analyses which are not impacted by the hazard ratios.

Comment 5: "Within the subgroup of stage III thoracic patients (n=69), those treated with UTT experienced a median extracranial TTP and OS of 19.3 months". What about patients without UTT?

Response: We now state on Page 11: "The median extracranial TTP among stage III thoracic patients not receiving UTT was 9 months."

Comment 6 - Do you collected toxicity secondary to WBRT + SRS versus SRS alone?

It would be interesting to add it when you report data about patients who received upfront WBRT with SRS (page 11)

Response: We did not reliable collect this toxicity data unfortunately.

Comment 7 - How many patients received systemic therapy alone? It is not referenced in text

Response: The text now states: "Among those not undergoing UTT, 31 received systemic therapy alone."

Comment 8 "Salvage therapy":
- Of the 78 patients who experienced extracranial progression, 41 received salvage systemic therapy or palliative radiotherapy to the chest. What about the rest? SBRT? None?

Response: We now specify that those 41 patients were treated at our institution and state: "The remainder of patients were either treated elsewhere or did not undergo additional therapy."

Comment 9. Discussion:
- Another limitation may be the PET staging of 68% of patients. The use of other techniques such as CT may under-diagnose patients.

Response: We have added to the discussion on limitations on Page 19: "Close to one-third of patients did not undergo PET for staging, which would be unlikely to occur presently."

Comment 10 - Due to the expected future and developments in NSCLC with regard to immunotherapy/targeted therapy, it would be interesting to mention perspectives or some literature in the discussion (e.g. PACIFIC trial shows increased overall survival and PFS in stage III NSCLC with Durvalumab [Faivre-Finn C, Vicente D, Kurata T, et al. Four-Year Survival With Durvalumab After Chemoradiotherapy in Stage III NSCLC-an Update From the PACIFIC Trial. J Thorac Oncol. 2021 May;16(5):860-867. doi: 10.1016/j.jtho.2020.12.015]).

We have not added on Page 19-20: "The improved PFS and OS associated with adjuvant immunotherapy after definitely concurrent chemoradiation for Stage III NSCLC REF suggest that definitive radiotherapy could also benefit patients with limited metastatic disease receiving immunotherapy."

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