Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-23-1435

Reviewer A

Comment 1: On line 104 the authors describe using MRI when brain metastases were "suspected or when a recurrence occurred." This is a bit misleading in that recurrences could have occurred but not been detected as there were no clinical symptoms. As MRI was not used routinely (which arguably would not have been standard of care outside of a prospective protocol) it is not feasible to know the true incidence of brain metastases. Presumably it would have been much higher (and some patients likely died with undetected brain metastases). The authors should discuss this as a major limitation.

Reply 1: Thank you for your suggestions. We apologize for the inaccurate description. What we really mean is that when a recurrence was indicated by symptoms or radiological examinations, a brain MRI would be performed for restaging.

Changes in the text: We have changed "Brain imaging was not routinely performed during follow-up and was only done when BM were suspected or when a recurrence occurred" to "Brain imaging was not routinely performed during follow-up and was only done when BM or a recurrence were suspected" (see Page 5, line 15-16) and discussed this issue as a major limitation as advised (see Page 12, line 9-11).

Comment 2: Concurrent chemoradiotherapy for Stage II-III NSCLC has been an accepted standard of care decades. It is unclear why only 21 of 134 patients received concurrent chemoradiotherapy.

Reply 2: We gratefully appreciate your valuable comment. As you said, concurrent chemoradiotherapy has been the standard of care for unresectable locally advanced NSCLC for a long time. However, many elderly patients, or those with comorbidities, were unable to tolerate concurrent chemoradiotherapy. A population-based study showed that nearly 60% of patients were theoretically not eligible for concurrent chemoradiotherapy (1). Restricted access to concurrent chemoradiotherapy is another problem that keeps patients from using it. Reported proportions of stage III NSCLC patients treated with concurrent chemoradiotherapy are 35%-55% in Europe and 78% in the US (2, 3). While in

China, the application of concurrent chemoradiotherapy is generally lower. Sequential chemoradiotherapy is widely used in clinical practice worldwide as an alternative to concurrent chemoradiotherapy.

In our study, 16% of patients were treated with concurrent chemoradiotherapy, while 80% and 5% of patients were treated with sequential chemoradiotherapy and only radiotherapy, respectively. The reasons for patients not using concurrent chemoradiotherapy in our study included PS of 2, severe comorbidities, the elderly, and doctors' preference. In fact, the utilization of sequential chemoradiotherapy still represents an important treatment modality in China. One important factor that results in this phenomenon is the inherent idea that intensification of both radiotherapy and concurrent chemotherapy may lead to excessive toxicity or incomplete treatment, and sequential chemoradiotherapy may be more suitable for frail patients who are less tolerant of concurrent (4). It has been reported that concurrent chemoradiotherapy may lead to an increased risk of toxicities such as radiation pneumonia and radiation esophagitis(5).

Changes in the text: We have added explanations of this issue (see Page 11, line 21-26) and deleted it from limitations in the Discussion section (see Page 12, line 4-6).

Comment 3: Only 11 of 134 patients developed brain metastases without a preceding or concurrent recurrence outside of the brain. Arguably, local, regional and non-brain distant recurrences can seed brain metastases. So many of the analyses (cumulative incidence of brain metastases, risk factors for brain metastases) are surrogates for analyses of any recurrence. In a retrospective analysis this is challenging to sort out. While separate analyses of the 11 patients with first/only recurrence of brain metastases could be considered, the numbers would be small, and it is possible that a subset of these 11 had undiagnosed extracranial progression. At a minimum, this should be discussed as a limitation.

Reply 3: We appreciate for your constructive comments. Considering the small number of patients with first/only recurrence of brain metastases and the fact that the results may be unreliable, the separate analyses were not conducted. We added this as a limitation in the text as advised.

Changes in the text: We discussed this issue as a limitation in the Discussion section according to your suggestion (see Page12 line 11-15).

Comment 4: The first 2 sentences of the discussion are repetitive with what is in the introduction. Perhaps the discussion should start with the most important findings.

Reply 4: Thank you for your valuable suggestion.

Changes in the text: We have removed the first 2 sentences and began the discussion with "PCI and MRI surveillance are two management strategies for BM, but both have not been recognized as standards of care for LA-NSCLC" (see Page 9, line 9-13).

Comment 5: The first paragraph discussed brain metastases prevention, but the reality is (and the authors summarize this well) no study of PCI has shown this to be of benefit. Also, for most of the patient who develop brain metastases, it is not clear that prevention is feasible. If the brain metastases are seeded from extracranial progression, then PCI would not have afforded any benefit. The concept of better screening of patients is better supported by their data and other studies.

Reply 5: Thank you for your positive comments and valuable suggestions to improve the quality of our manuscript.

Changes in the text: None.

Comment 6: I will admit to not understanding Figure S1. I don't think I have seen an ROC curve where the curve trends in positive and negative directions along the x axis. Is this correct?

Reply 6: We apologize for our carelessness. We used "false positive rate" and "true positive rate" as the labels of the x and y axes, which are equal to "1-specificity" and "sensitivity", respectively.

Changes in the text: We changed the labels of the x and y axes to "1-specificity" and "sensitivity" to make them consistent with the common form of ROC labels (see Figure S1).

Reviewer B

Comment 1: Why include 2 stage IIB pts? This is not LA-NSCLC and has a relevant different prognosis from stage III disease - I would exclude them.

Reply 1: Thank you for your question. In our study, stage IIB patients were included based on the following several considerations. Firstly, to the best of our knowledge, the definition of locally advanced NSCLC is rather ambiguous. Although locally advanced NSCLC is used to refer to stage III NSCLC in most research, stage II patients are also included in locally advanced NSCLC patients according to NCCN guidelines (6) and in some other studies(7, 8). Secondly, for patients with stage II-III NSCLC, the prevention of brain metastases using PCI

remains a controversial issue(9). Thirdly, conventional fractionated radiotherapy is an important curative therapeutic option for inoperable stage IIB NSCLC(10).

Changes in the text: None.

Comment 2: EGFR mutation is too heterogeneous definition; which type? common? ex 20 ins? uncommon? compound? mixed? specify also in the table of pts characteristics

Reply 2: Thank you for your suggestions. We agree that the types of EGFR mutations are important and should be specified. 48 patients with adenocarcinoma in our study were tested for EGFR mutation, and 17 of them were EGFR mutation positive. The Exon 19 deletion and L858R point mutation were detected in 8 and 7 patients, respectively. Uncommon mutations were detected in 2 patients (1 with exon 20 insertion and 1 with G719X).

Changes in the text: We have added the description of specific types of EGFR mutations to the table of baseline characteristics (see Table 1). Besides, we added the description of EGFR mutation status in the first paragraph of the Results section (see Page 7 line 5-8) and modified that in the subgroup results (see Page 8 line 24-28).

Comment 3: The authors calculate the risk of brain mets: however is not clear how and if subsequent systemic treatment might have had an impact on this especially in the few cases (no. 6) in which brain was not the first site of relapse. Do the authors have this information

Reply 3: Thanks for your valuable comments. We agree that the subsequent systemic treatment may influence the development of BM. In our study, 88 patients experienced recurrences; of these, 69 did not have their first failure occur in the brain. Of the 69 patients, 15 received PD-1/PD-L1 immunotherapy after their first recurrence, either in combination with or without chemotherapy; 3 patients received EGFR-TKIs; 25 received single-agent or double-agent chemotherapy; 3 patients did not receive any anti-tumor therapy; and 23 patients' subsequent systemic treatment information was missing for various reasons. As for the six patients who developed brain metastases but not as the first site of relapse, two of them received chemotherapy, one patient received osimertinib, and the remaining three were unknown. Considering the incomplete information about subsequent systemic treatment, its impact was difficult to clarify. And we added it as a limitation to the Discussion section (see Page12 line 15-17).

Changes in the text: We added the incomplete data of subsequent systemic treatment as a limitation to the Discussion section (see Page12 line 15-17).

Comment 4: Was PD-L1 assessed? was any other biomarker assessed? What was the method for the assessment of EGFR mutation?

Reply 4: Thanks for your questions. Out of the 134 patients in our study, only 68 were tested for PD-L1 expression. For patients with known PD-L1 expression levels, we performed separate analyses using cut-offs for PD-L1 expression levels of 1%, 10%, 50%, and 90%. The univariate competing risk regression revealed that the PD-L1 expression levels have no impact on brain metastasis development (all p values > 0.1). Considering the incomplete data and the above findings, we decided not to include them in the text. Additionally, we did not evaluate any other biomarkers that were not mentioned in the article. The molecular pathology associated with EGFR mutations was evaluated using polymerase chain reaction-based assay. And we have described that in the fourth paragraph of the Methods section (see Page 5 line 29-30).

Changes in the text: None.

Comment 5: in the abstract under methods the authors say that pts could receive or not PCI, but no mention has been done in the text. Was this the case of some pts? I would caution the authors when talking of PCI in this group of pts which is far from being standard, rather if risk factors are identified more intensive brain imaging could be offered for early detection.

Reply 5: We apologize for the misleading description. What we mean to say in the abstract is that enrolled patients must not have received PCI. And we stated that as a criterion for exclusion in the first paragraph in the Methods section (see Page 4 line 24).

Changes in the text: We deleted "without prophylactic cranial irradiation (PCI)" from the abstract (see Page 2 line 8-9), considering that PCI was rarely performed in clinical practice and that it might cause misunderstanding. And we retained patients who received PCI as an exclusion criterion in the text (see Page 4 line 24).