Peer Review File
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Reviewer A

The authors report the results of 571 surveys regarding first-line treatment of brain metastases which show that there is large variability in practice especially depending on medical subspecialty.
Several suggestions for the manuscript:
Comment 1: It is important to recognize that the percentage of responders relative to the number of individuals approached is very small and may therefore in fact not fully represent the true picture of practice. in addition, the majority of responders are in academic practice which could skew the data even further. this needs to be noted in the discussion
Reply 1: We have added this in the discussion on page 17 line 362.
Changes in text: See the text as described.

Comment 2: Significant heterogeneity in practice could also be accounted for by the difference in countries in which the respondents practice with access to differing modalities possibly differing across countries. the fact that only 58% of COs versus 93% of MOs have access to ALK inhibitors highlights this fact. perhaps it would be helpful to report the results by region also and break down the results by which practitioners consult ASCO and ASTRO guidelines in their practice
Reply 2: These data were not included in the final manuscript as detailed information regarding access issues (i.e. regional variations in payment / reimbursement for drugs, access programs from pharmaceutical companies, etc) to particular medications was not captured and out of the scope of the intended study.
Changes in text: None.

Comment 3: heterogeneity in practice could also be affected by experience given that COs and MOs see less than 3 cases per month of new brain metastases versus the majority of NS and RO seeing 3-10 cases.
Reply 3: Agree.
Changes in text: None.

Comment 4: when analyzing the data, it would seem that based on the figures, there might be more similarity between CO and RO than CO and MO especially since COs have access to radiation tools also. perhaps better subanalysis could be MO alone versus CO/RO versus NS?
Reply 4: Although this may seem to be true for figure 2A and 2D, it was not the case for the remainder of the analyses and therefore, the overall analysis was not adjusted.
Changes in text: None.

Reviewer B

This is an interesting and well-written manuscript describing the practice patterns of clinical/medical oncologists, radiation oncologists, and neurosurgeons regarding their approach to EGFR- and ALK-positive lung cancer with brain metastases. As treatment modalities evolve for EGFR and ALK-positive lung cancer and newer, CNS-penetrant TKI therapies emerge, it is timely to understand the different practices of various subspecialists involved in the care of these patients. While the study offers valuable information, I also have the following comments and suggestions:

Comment 1: Although I was glad to see that the authors acknowledged this limitation in their Discussion, I noted while reading the Methods and Results that the analysis would have benefitted from a more nuanced look at practice patterns according to the type of TKI therapy (osimertinib/alectinib versus older-generation, less CNS-penetrant agents) and radiation (WBRT vs SRS) used. The emergence of CNS active therapies like osimertinib, alectinib, brigatinib, and lorlatinib has made many of us feel more comfortable using these therapies alone, especially in the case of asymptomatic or small volume brain metastases. In addition, if only WBRT is an option (eg, if there are innumerable but small CNS lesions that cannot be radiated with SRS alone), this similarly changes how we think about the addition or radiation or not. Assessing practice patterns without accounting for these variables is a significant methodologic downside and misses the opportunity to explore differences among subspecialists in a nuanced and clinically-relevant way. In addition, it likely would have been easy to include a question in the radiation oncology survey to query which radiation modality (SRS vs WBRT) providers recommend for <4, 4-9, and >9 metastases.

While there may not be a way to add this information at this point, I did note that the survey asked medical and clinical oncologists about which TKI therapy they used or had available in the first-line setting. It would be helpful if the authors could include responses from this question in their study as this would provide context for the clinical/medical oncology responses to the clinical scenarios.
Reply 1: As discussed in the manuscript, newer generation agents were not available when this study was conducted. Moreover, only a few of respondents reported precise information of the exact agents available in clinical practice and therefore this data was not included.
Changes in the text: None.

Comment 2: In the Discussion section, the authors describe analyses from Magnussen et al and Thomas et al when reviewing data on survival for TKI therapy alone versus TKI therapy with radiation. A discussion of these studies should acknowledge the different TKI populations that each one evaluated (erlotinib in 98% of patients in Magnussen et al versus all newer-generation, CNS-penetrant therapies [osimertinib, alectinib, etc] in Thomas et al). This puts the results into context and potentially explains the different outcomes across the two studies.
Reply 2: Good comment / suggestion. We have updated our manuscript.

Changes in the text: Page 16, line 333.

Comment 3: What was the rationale for selecting the societies whose members were queried for the survey? What was the rationale for not selecting certain other societies such as ASCO or IASLC?
Reply 3: No specific inclusion and/or exclusion criteria were used.
Changes in the main text: None.

Comment 4: In accounting for the differences in responses between the subspecialties, it is notable that clinical and medical oncologists tended to be more likely to have fewer years since starting practice. It is possible that these younger physicians may have been more familiar with the newer-generation TKI therapies given their proximity to fellowship training. Consider commenting on this explicitly in the Discussion.
Reply 4: This is an interesting point. However, it would be difficult to separate this data out and provide a meaningful sub-analysis given information about years in fellowship, number of time spent in specialized brain metastases clinics, etc. for each respondent was not collected and would be relevant to further interpret these data.
Changes in the main text: None.

Comment 5: I found it surprising that 42% of clinical oncologists reported not having access to ALK TKI therapies in their practice. What would account for this, and could it be that respondents when answering question 15 only noted and selected the EGFR TKI therapies and forgot to select ALK therapies?
Reply 5: Data on reasons / explanations for regional variation in drug access was not obtained and out of scope of this study. See repones A2.
Changes in the main text: None.

Comment 6: A few noted grammatical errors:
- Line 141 - remove "with"
- Lines 245-248 - repetitive sentences
Reply 6: Thank you for pointing this out. We have corrected these.
Changes in the main text: See respective lines 141 and 245.

Reviewer C

Comment: To ascertain practice variability among the multidisciplinary clinicians who are involved in first-line managements of EGFR mutant- or ALK fusion- NSCLC patients with asymptomatic brain metastases, the authors conducted an international survey among medical oncologists, clinical oncologists, radiation oncologists, and neurosurgeons. The report is generally clearly presented; however, the reviewer has some comments about the following point.

There are some differences of the tissue penetration rates including brain among several

TKIs. For example, the lack of blood–brain barrier permeability of 1st-generation EGFR-TKIs could be one of the reasons for their limited efficacy in the treatment of brain metastases, while preclinical studies indicate that the blood–brain barrier permeability of osimertinib was greater than the other EGFR-TKIs (Clin Cancer Res. 2021 Jan 1;27(1):189-201.). Furthermore, clinical study reported that osimertinib provided better clinical benefits to patients with brain metastases than those with the other EGFR-TKIs (BMC Cancer. 2022 Jun 14;22(1):654.). Therefore, the difference of the clinical efficacies of TKIs for patients with brain metastases should be considered when we conduct radiotherapy or surgery in the management of brain metastases. The reviewer recommends to refer these papers and discuss the management plans of brain metastases based on the difference of TKIs.
Reply: This is clearly addressed as a limitation in our study starting on line 343 and is discussed in considerable detail throughout the paragraph.
Changes in the main text: None.

Reviewer D

This report concerns a clinically important subject, however, some points should be addressed in order to further improve the manuscript:

Comment 1: lines 106-107: EGFR+ NSCLC patients "are nearly 4 times more likely to present with BrM compared to patients with non-EGFRm NSCLC (Ref. 2)" -> this is actually questionable, please note that there are larger studies with more clear data that show similar percentages of BM at baseline among EGFRmut, ALKmut and WT NSCLC, e.g. PMID 22282022 Figure 5D.
Reply 1: Thank you for pointing this out. We have removed the section.
Changes in the main text: See line 106.

Comment 2: lines 328-332: "In addition, a 2019 meta-analysis... (Ref. 25)" -> the coverage of the literature is rather selective here. In fact, there are several retrospective studies which show that RT in addition to TKI improves PFS, but not OS, e.g. PMID 34090172 and several others (e.g. PMID 30936745), therefore the PFS benefit from RT is consistent in older studies, but the OS benefit from RT is controversial. The subsequently cited Ref. 26 (Thomas et al JTO 2022) is a newer study (the first of its kind) which furthermore shows that with the newer, CNS-penetrant TKI (osimertinib for EGFR, as well as 2G/3G TKI for ALK) not even the PFS benefit of RT is evident any more. The wording should be modified here and the coverage of the literature should be improved.
Reply 2: The meta-analysis included 12 studies while PMID 34090172 and 30936745 are single centre studies. We agree with the point that this is controversial and hence the reason for our study and discussion about this being an issue. Nonetheless we have updated our discussion and added these citations.
Changes in the main text: See page 16 line 334-336.

Comment 3: Please also consider as a general limitation the fact that the particular molecular

features of the tumors were not considered, since there is some evidence that some particular oncogene variants are associated with a higher risk of brain progression and might require more aggressive management (non-del19 EGFRmut, and EML4-ALK variant 3, PMID 34090172).

Reply 3: We have added wording to acknowledge this.

Changes in the main text: Page 17, line 359.