Peer review file

Article information: https://dx.doi.org/10.21037/jtd-21-924

Reviewer A

Thank you very much for your review of our article and your valuable and constructive suggestions. I will answer your suggestions point by point in the following.

The authors performed a retrospective, single institution review of small (pT1a and pT1b) lung adenocarcinomas to evaluate the prognostic value of EGFR mutations with respect to recurrence and overall survival within this cohort. There have been many manuscripts written on this topic and most have concluded that EGFR mutant lung cancer has a similar, if not slightly improved, outcome than wild-type EGFR tumors. In addition, associations of EGFR mutant lung cancers with patient demographics, histologic subtypes, smoking status, etc. have all been previously described. Given the extensive literature on this topic there is not much new that this manuscript offers to the reader.

The authors found that while EGFR mutations were not prognostic with respect to recurrence, EGFR mutant lung adenocarcinoma had improved overall survival in comparison to EGFR wild-type patients on univariate analysis alone. They hypothesize may be related to treatment with TKIs following recurrence. However, while EGFR mutational status was prognostic for OS within multiple subgroups on univariate analysis, EGFR mutant lung adenocarcinoma in pstage IA1 or IA2/N1/2M0 was not associated with longer OS or RFS on multivariate analysis.

Comment 1: Given that there were only 16 patients with EGFR mutations that were not exon19 deletions or exon 21 L858R mutations these should be excluded from the dataset and not included. These mutations are not targetable currently and lumping all EGFR mutations together is not appropriate.

Reply 1: Unlike predictive markers, a prognostic marker is indicative of innate tumor behavior and patient survival independent of treatment administered. In this study, we

aimed to evaluate the prognostic significance of EGFR mutation status (prognostic marker) instead of predicting the effect of targeted therapy in patients with EGFR mutation (predictive marker). So we lumping all EGFR mutation together for analysis. In addition, we analyzed the prognostic significance of EGFR mutation status using the dataset only including exon19 deletions or exon 21 L858R mutations, and we found that there was no significant difference in RFS between different EGFR mutation types (Additional Files).
Changes in the text: NO.

Comment 2: Can the authors explain the rationale of including invasive mucinous adenocarcinoma patients? Though low in number (n=7), activating EGFR mutations are rare in this subtype and in this study 6/7 are EGFR wild-type and the remaining patient had neither an exon 19 deletion nor exon 21 L858R mutation? These patients should be excluded from the analysis and the manuscript.

Reply 2: In this study, we collected all the mutation data of invasive adenocarcinoma including the subtype of invasive mucinous adenocarcinoma in order to investigate the prognostic value of EGFR in invasive adenocarcinoma instead of analyzing the effect of targeted therapy. So we included invasive mucinous adenocarcinoma patients.
Changes in the text: NO.

Comment 3: The authors hypothesize that OS (in the KM curves) was significantly extended in patients with EGFR mutations which they speculate may be attributed to TKI treatment, as there was no prognostic value in terms of RFS. With very small numbers (N=27) they also demonstrate that patients with recurrence of their EGFR mutant lung adenocarcinoma treated with TKIs have the best survival, EGFR mutants without TKI's still had better outcomes than EGFR wild type patients 63% 5-y OS vs 42%). Can the authors provide any hypothesis as to why this may be the case and describe the characteristics of the 18/45 EGFR mutant patients with recurrence who were not treated with TKIs?

Reply 3: In this study, we found that patients with EGFR mutation had better OS than

patients with wild type EGFR in univariate analysis in the entire cohort, so we further hypothesized that the outcome could be accounted for the therapy of TKIs. However, we conducted this analysis on univariate analysis alone, so we deleted this result considering the rigor of results. In 2009, Kosaka and colleagues analyzed 397 patients with surgically resected stage I to IV lung adenocarcinomas and without any treatment of EGFR-TKIs. They also found that patients with EGFR mutations had better OS than those without mutations(P=0.005) in univariate analysis, but the survival difference did not approach significance in multivariate analysis, the molecular mechanism behind this is still unclear. It may need more clinical and basic research to discover the underlying mechanism for this result. The characteristics of the 18/45 EGFR mutant patients with recurrence who were not treated with TKIs were added in the text.
Changes in the text: we have modified our text as advised (see Page 3, line 46-48; Page 7, line 147-152; Page 11, line 226-227).

Comment 4: I do not believe that TKI therapy following recurrence was accounted for in any of the overall survival analyses. The authors hypothesize that this makes a difference in OS, but in fact they show it doesn't as shown on subsequent MVA. I do not think the authors can have it both ways – hypothesizing that treatment with TKI improves OS (again with very, very small numbers), while concomitantly showing it doesn't on MVA. While I believe (with much larger numbers) that TKI therapy may improve OS, the data provided here does not show that.

Reply 4: I'm agree with your opinion. Indeed, although the EGFR mutant patients with TKIs had the best OS, EGFR mutant patients without TKIs still had better outcomes than EGFR wild type patients in this study. Therefore, TKI therapy following recurrence could improve OS instead of accounting for in any of the overall survival analyses. So we deleted this result and conclusion.
Changes in the text: NO.

Comment 5: How was recurrence defined and what were the recurrence patterns?

Reply 5: Recurrence was defined as local recurrence and distant recurrence, and the recurrence patterns were added in the text.
Changes in the text: We have modified our text as advised (see Page 5, line 104-105 and Page 7, line 136-139).

Comment 6: There were 56 (17% of cohort) patients with node-positive disease. Did any of these patients receive adjuvant chemotherapy or radiation or a TKI? What was the prognostic significance of EGFR mutation status within the pN1-2 cohort?

Reply 6: Some patients with node-positive disease received adjuvant chemotherapy or radiation. There was no prognostic significance of EGFR mutation status for RFS within the pN1-2 cohort (P=0.641).
Changes in the text: We have modified our text as advised (see Page 7, line 139-141).

Reviewer B

Chen et al. included 338 patients with pathological T1a and T1b invasive lung adenocarcinoma with EGFR information who underwent radical resection into their study. The authors found that EGFR mutation status did not affect the recurrence-free survival but did affect the overall survival, which might be due to the therapeutic effect of tyrosine kinase inhibitors (TKIs). The clinical message of this study is well-focused, and the conclusion is informative. The clinical impact of this study should be the fact that the therapeutic efficacy of TKIs would be well demonstrated even after recurrence has occurred. Adjuvant use of TKIs has been discussed well recently, however, the use of TKIs after recurrence might be enough to have sufficient therapeutic efficacy. There are several points to be addressed.

Comment 1: Do you have any information on pathological spread through air spaces (STAS)? STAS has been an emerging prognostic factor in lung cancer recently. Information on STAS would be desirable if it is available.

Reply 1: NOT available.
Changes in the text: NO.

Comment 2: In the OS analyses, EGFR mutation status was not a significant prognostic factor in multivariate analyses (Table2 and 3). How do you interpret it?

Reply 2: The prognostic value of EGFR mutation status could be covered by the more powerful prognostic factors such as pN stage and the radiologic appearance.
Changes in the text: NO.

Comment 3: The use of the 8thedition of the UICC TNM classification should be described in Methods section.

Reply3: We have modified our text as advised.
Changes in the text: We have modified our text as advised (see Page 5, line 98-99).

Comment 4: Does “pathological tumor size” in Table 1 show the size of only invasive area, or the total tumor diameter?

Reply 4: The total tumor diameter.
Changes in the text: NO.

Comment 5: Some misspellings: “range” at line 144, “there” at line 188, “Lin” at line 209, “accounted” at line 237, and “predicting” at line 241.

Reply 5: We have modified our text as advised.
Changes in the text: We have modified our text as advised (see Page 8, line 169; Page 9, line 186; Page10, line210, 213).