Peer Review File

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Reviewer A

Comment 1: The situation of "untreated" EGFR mutant group is beyond my understanding. Why did they receive Tx, such as chemotherapy, or TKI or others. Actually 365 cases were treated by TKI. Correct the abstract.

Reply 1: Thanks for your comment. We delete the incorrect word "untreated".
Changes in the text: In our research, 365 NSCLC patients with EGFR mutation (EGFR-mutant group), who were not resistant to first-generation EGFR TKI and 316 first-generation EGFR TKI resistant NSCLC patients harboring with T790M mutation (T790M-mutant group) were retrospective studied. (see page 4, line 85-88)

Comment 2: Give the readers of EGFR mutants concretely such as exon 19 deletion and L858R and other minor ones IN the text. I noticed in Table.

Reply 2: Thanks for your comment. We added the EGFR mutations concretely in the text.
Changes in the text: However, some patients may have a mutation that substitutes methionine for threonine at amino acid position 790 (T790M) after being treated with first generation TKI [13]. (see page 6, line 187-189)
And before treatment, all of them harbored EGFR mutant, such as exon 19 deletion (19 DEL), substitutions of leucine for arginine (L858R) in exon 21. 316 patients were diagnosed from Feb, 2001 to Dec, 2016. (see page 6,7, line 206-207,230)

Comment 3: The definition of resistance is not clear. First generation TKI was continued even they have brain metastasis and bone metastasis and that was not resistance.

Reply 3: Thanks for your comment. We added the definition of resistance.
Changes in the text: T790M mutation inhibits the binding of first-generation TKI to its binding site and the resistance to first-generation TKI arises. Some reviews have illustrated the mechanism of the relationship between the T790M and the development of resistance to first-generation TKI [14, 15]. (see page 6, line 189-

192)

Comment 4: It is remarkable only 54 % were adenocarcinoma in EGFR mutation group. I am not sure this is the ordinary prevalence in Asian populations.

Reply 4: Thanks for your comment. Since there was not enough tissue in some patients, the pathological subtype of these patients was tested by cytology rather than immunohistochemistry. And the test results only suggested NSCL. So the pathological subtype of these patients were not sure.
Changes in the text: And 54.2% of them were adenocarcinoma. The pathological results of 23.8% patients only suggested NSCLC, since some patients were just tested by cytology rather than immunohistochemistry. (page 8, line 263-266)

Comment 5: Just give the readers T790M were routinely tested in all the cases during the course. It is not reasonable all the resistances are caused by T790M. How much of resistance cases had T790M (I know 316 cases were T790M).

Reply 5: Thanks for your comment. Our research included only those who were resistant to first-generation TKI and with T790M mutation. And in our institution, 50% of the patients who were resistant to first-generation TKI had T790M mutation.

Reviewer B

Comment 1: intro "About 30-40% of NSCLC patients present with metastases at the time of diagnosis [6]." >> Please note the rate was reported as 47% in ref-6 [Mol Clin Oncol. 2015 Jan;3(1):217-221]

Reply 1: Thanks for your comment. It was mentioned in the introduction part that approximately 30–40% of NSCLC patients present with metastatic disease at the time of diagnosis in the ref-6[Mol Clin Oncol. 2015 Jan;3(1):217-221]. Since the rate 30%-40% was quoted from other references, we think it is better to revise the rate as it was reported in ref-6.
Changes in the text: In the study of Tamura et al., 47.3% of NSCLC patients present with metastases at the time of diagnosis [6].
(see page 5, line 173-174)

Comment 2: method "Data was collected retrospectively from the clinical process of patients with lung cancer and metastases who were diagnosed" >> The detection of

asymptomatic metastasis depends on the routine work-up [eg, were brain image or bone scan routine?], so please specify the routine work-up in the authors' institute.

Reply 2: Thanks for your comment. We specified the routine work-up in the article. Changes in the text: After admission, systemic bone image, brain MRI, abdominal MRI or color Doppler ultrasonography and chest computed tomography (CT) were performed on patients diagnosed with lung cancer every six to eight weeks in case of metastasis. (page 6, line 203-205)

Comment 3: method "316 patients were diagnosed from Feb, 2001 to Dec, 2016. They were with T790M mutation after treated with first-generation EGFR-TKI. Another 365 patients were diagnosed from June 2018 to May 2019 and they were all treated with the first-generation EGFR TKI. But unlike the last 316 patients, these patients didn't get resistance to the first-generation EGFR TKI when we analyzed the data" & result "We obtained the metastasis time in months of T790M mutant group by calculating the length of time between the confirmed diagnosis date and the metastasis date" >> For the 1st group [n=316], were all patients without T790M mutation at the time of initial use of 1st generation TKI? By the way, please specify the exact types of 1st generation TKI [gefitinib and erlotinib?].

Reply 3: Thanks for your comment. In the T790M mutation group, all the patients were without T790M mutation at the time of initial use of 1st generation TKI. And the exact types of 1st generation TKI were specified in the text.
Changes in the text: 316 patients were diagnosed from Feb, 2001 to Dec, 2016. They were with T790M mutation after treated with first-generation EGFR TKI, such as erlotinib and gefitinib. (page 7, line 230-232)

Comment 4: method "Some patients suffered from two or more metastases and were independently analyzed in each metastatic site" >> please provide reference[s] to justify this independent assumption.

Reply 4: Thanks for your comment. The method of the article was based on following references.

1. Riihimäki, M., et al., Metastatic sites and survival in lung cancer. Lung Cancer, 2014. 86(1): p. 78-84.
2. Tamura, T., et al., Specific organ metastases and survival in metastatic non-small-cell lung cancer. Mol Clin Oncol, 2015. 3(1): p. 217-221.
3. Rosell, R. and N. Karachaliou, Relationship between gene mutation and lung cancer metastasis. Cancer Metastasis Rev, 2015. 34(2): p. 243-8.

Changes in the text: Some patients suffered from two or more metastases and were respectively analyzed in each metastatic site. (page 7, line 241-242)

Comment 5: table 3. The time window for metastasis development was different for these two groups [AFTER resistance to 1st generation TKI in T790M group vs BEFORE resistance to 1st generation TKI in EGFR group] so the comparison in table 3 was less meaningful.

Reply 5: **Thanks for your comment. Through table 3, we found that lung cancer patients with T790M were more likely to have metastases, especially brain metastases, bone metastases, liver metastases, and intrapulmonary metastases, which was meaningful to certify that T790M mutation was related to metastases.**

Reviewer C

Comment 1: In the materials and methods, it mentioned that "Some patients suffered from two or more metastases and were independently analyzed in each metastatic site." （page 11）I think this way of analysis will affect the comparison in Table III .

Reply 1: **Thanks for your comment. The chi-square in table 3 was to work out the relationship between T790M and individual metastatic site. And the results showed lung cancer patients with T790M were more likely to have metastases, especially brain metastases, bone metastases, liver metastases, and intrapulmonary metastases.**

Comment 2: Death due to some other non-lung cancer disease has not been discussed. So, I am afraid that the conclusion that most metastases were related to EGFR positive mutant or T790M mutation but not to the survival time, is not convincing enough.

Reply 2: **Since this was a retrospective study, we focused on the metastasis time, and the death reason was not emphasized. Next, we will do prospective study based on this comment.**

Comment 3: The language needs to further polished.

Reply 3: **The language has been polished.**
Changes in the text: