occurred in separate cellular clones. The level of the C797S mutation is expected to be similar to or lower than the level of the T790M mutation if both mutations are present in the same cells, and it would show either concomitant increase or decrease in response to the combination therapy. The levels of each *EGFR* mutation measured by digital droplet polymerase chain reaction from a series of plasma samples indicated that the T790M and C797S mutations were likely present in different tumor cells, a finding that as we suggested in our article, may be due to multiple clones with individual mutations and resultant differences in tyrosine kinase sensitivity.[3]

In the blood collected before the combination therapy, the levels of the T790M and C797S mutations were detected at mutant allele frequencies of 2.8% and 4.5%, respectively. This indicates that the overall load of C797S-positive tumor was higher than that of T790M-positive tumor before the combination therapy. The observed clinical improvement without reduction in T790M or exon 19 deletion also supports this hypothesis of clonal heterogeneity rather than the mutation being present in the same cells. Definitive proof, however, would require single-cell analysis, which is not possible for this patient.

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Comments on "Treatment Strategies and Prognostic Factors of Limited-Stage Primary Small Cell Carcinoma of the Esophagus"

To the Editor:

We read with great interest the article by Xu et al.[1] After reading this article carefully and critically, we noticed some methodological and statistical issues that were not addressed or mentioned as limitations of the study. We therefore wish to highlight a few important take-home messages as follows.

First, the study population consisted of patients who visited and were treated in a tertiary care center.[2] Here, the validity of the results may be threatened by selection bias because the recruited participants comprised a nonrandom sample from the target population. Such selection bias is defined as recruitment or referral bias.[3] This bias stems from the fact that patients who participated in the study may differ from those who did not participate in the study. For example, people who are referred to a tertiary care center may have characteristics (e.g. socioeconomic status) different from those of people who are not. Therefore, the estimated survival of patients with primary small cell cancer of the esophagus may reflect a degree of selection bias.

Therefore, we recommend that the authors report the background characteristics of the patients in detail. In addition, they could adjust for the effect of these characteristics on survival by including them in the multivariable analysis as confounders. Moreover, there are statistical methods for conducting bias analysis to determine how much the results are influenced by selection bias.[4]

Disclosure: The authors declare no conflict of interest.

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ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2017.10.026

Second, as a more general principle, the multivariable model is developed after a univariate screening for statistically significant predictors. We are concerned as to why the authors did not use univariate analysis for selecting the significant predictors for their multivariable model. On the other hand, how they did their multivariable analysis is unclear. The stepwise method is a commonly used approach for model building in biomedical research. It may be argued that the value of regression coefficients is highly reliant on univariate prescreening of variables and type of multivariable analysis.[5,6]

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Response to "Comments on Treatment Strategies and Prognostic Factors of Limited-Stage Primary Small Cell Carcinoma of the Esophagus"

In Response:

We would like to thank Safiri et al. for their interest in our article and for their helpful comments.[1] We have carefully reviewed both the comments and our article and the following is our response.

First, we retrospectively analyzed the data on 152 consecutive patients with limited-stage primary small cell carcinoma of the esophagus (PSCCE) who received treatment at the Affiliated Cancer Hospital of Zhengzhou University.[2] Safiri et al.[1] mentioned that the included patients were treated in a tertiary care center and that selection bias may exist. This bias may be because the patients included in our study may differ from those who did not participate in our study in terms of having different characteristics, such as socioeconomic status. Because of the retrospective nature of this study, this bias cannot be avoided. The People's Republic of China is large-population country with thousands of subordinate hospitals, and currently we do not have the information for patients with PSCCE in subordinate hospitals. In this study, only 152 consecutive patients could be evaluated retrospectively. However, the comment of Safiri et al. could be a valuable starting point for future research. We are planning to initiate a multicenter study to collect patient information as comprehensively as possible in the near future.

Safiri et al.[1] stated that the authors should have better reported the background characteristics of the patients in

Disclosure: The authors declare no conflict of interest.

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ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2017.11.120