

Instead, we compared the rates of response to LCBI and salvage chemotherapy after immunotherapy after dividing chemotherapy regimens into pemetrexed/platinum, taxane based, gemcitabine based, and others.

In conclusion, though it is a retrospective study with a small number of subjects, we think that our study was well conducted with reasonable methods and provides clinical evidence for future prospective trials that will investigate the improved clinical outcomes of salvage therapy after immune checkpoint inhibitors.

**Jong-Mu Sun, MD, PhD**

Division of Hematology-Oncology  
Department of Medicine  
Samsung Medical Center  
Sungkyunkwan University School of Medicine  
Seoul, Republic of Korea

## References

1. Costantini A, Cadranel J. Increased response rates to salvage chemotherapy administered after PD-1/PD-L1 inhibitors in patients with non-small cell lung cancer. *J Thorac Oncol.* 2018;13:e55-e56.
2. Park SE, Lee SH, Ahn JS, Ahn MJ, Park K, Sun JM. Increased response rates to salvage chemotherapy administered after PD-1/PD-L1 inhibitors in patients with non-small cell lung cancer. *J Thorac Oncol.* 2018;13:106-111.
3. Yang CH, Simms L, Park K, Lee JS, Scagliotti G, Orlando M. Efficacy and safety of cisplatin/pemetrexed versus cisplatin/gemcitabine as first-line treatment in East Asian patients with advanced non-small cell lung cancer: results of an exploratory subgroup analysis of a phase III trial. *J Thorac Oncol.* 2010;5:688-695.
4. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol.* 2008;26:3543-3551.
5. Sun JM, Ahn JS, Jung SH, et al. Pemetrexed plus cisplatin versus gemcitabine plus cisplatin according to thymidylate synthase expression in nonsquamous non-small-cell lung cancer: a biomarker-stratified randomized phase II trial. *J Clin Oncol.* 2015;33:2450-2456.
6. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med.* 2016;375:1823-1833.
7. Grigg C, Reuland BD, Sacher AG, Yeh R, Rizvi NA, Shu CA. Clinical outcomes of patients with non-small cell lung cancer (NSCLC) receiving chemotherapy after immune checkpoint blockade [abstract]. *J Clin Oncol.* 2017;35(suppl 15):9082.
8. Leger PD, Rothschild S, Castellanos E, Pillai RN, York SJ, Horn L. Response to salvage chemotherapy following exposure to immune checkpoint inhibitors in patients with non-small cell lung cancer [abstract]. *J Clin Oncol.* 2017;35(suppl 15):9084.

## Comments on Prognostic Impact of Margin Distance and Tumor Spread through Air Spaces in Limited Resection for Primary Lung Cancer



hazard ratio (HR) of 12.24 (95% confidence interval [CI]: 2.61–57.37) and, moreover, lymph vessel invasion is associated with distant recurrence (HR = 8.36, 95% CI: 1.67–41.87).<sup>1</sup> Although the results were very interesting, some methodological issues should be considered.

It argued that relatively large effect estimate and imprecise CI may be obvious indicators of sparse data bias.<sup>2–4</sup> In other words, there are inadequate data for combination of predictor and outcome levels.<sup>2</sup> Here, we are concerned that the estimated HRs (and 95% CIs) for spread through air spaces and lymph vessel invasion may be biased because of sparse data bias.

Another important reason for imprecise CI for estimate coefficients is presence of collinearity among the studied predictors. As a general rule, collinearity among the predictors will be checked before regression analysis by using variance inflation factors.<sup>5</sup>

The authors did not attempt to check the proportional hazards assumption before Cox regression analysis. As shown in the Figure 1 of Masai et al,<sup>1</sup> it may be that the proportional hazards assumption is violated

### To the Editor:

We read with great interest the study by Masai et al.<sup>1</sup> The authors mentioned that spread through air spaces is associated with local recurrence with a

**Disclosure:** The authors declare no conflict of interest.

Address for correspondence: Saeid Safiri, PhD, Managerial Epidemiology Research Center, Department of Public Health, School of Nursing and Midwifery, Maragheh University of Medical Sciences, Maragheh, Islamic Republic of Iran. E-mail: saeidsafiri@gmail.com

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for relapse-free survival curves for local recurrence of patients undergoing limited resection according to the studied variables.

Finally, it seems that there is degree of referral bias in the estimated associations on account of selection of patients referred to the National Cancer Center Hospital for the study.

**Kamyar Mansori, MSc**  
Social Determinants of Health Research Center  
Kurdistan University of Medical Sciences  
Sanandaj, Islamic Republic of Iran  
Department of Epidemiology  
School of Public Health  
Iran University of Medical Sciences  
Tehran, Islamic Republic of Iran

**Erfan Ayubi, PhD**  
Department of Epidemiology  
School of Public Health  
Shahid Beheshti University of Medical Sciences  
Tehran, Islamic Republic of Iran  
Department of Epidemiology and Biostatistics  
School of Public Health  
Tehran University of Medical Sciences  
Tehran, Islamic Republic of Iran

## Response to Letter to the Editor Titled “Comments on Prognostic Impact of Margin Distance and Tumor Spread through Air Spaces in Limited Resection for Primary Lung Cancer”



### **In Response:**

We would like to thank Mansori et al.<sup>1</sup> for their interesting and thoughtful comments on our article “Prognostic Impact of Margin Distance and Tumor Spread through Air Spaces in Limited Resection for Primary Lung Cancer.”<sup>2</sup>

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Address for correspondence: Noriko Motoi, MD, PhD, Division of Pathology, Department of Pathology and Clinical Laboratories, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: [nmotoi@ncc.go.jp](mailto:nmotoi@ncc.go.jp)

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**Saeid Safiri, PhD**  
Managerial Epidemiology Research Center  
Department of Public Health  
School of Nursing and Midwifery  
Maragheh University of Medical Sciences  
Maragheh, Islamic Republic of Iran

## References

1. Masai K, Sakurai H, Sukeda A, et al. Prognostic impact of margin distance and tumor spread through air spaces in limited resection for primary lung cancer. *J Thorac Oncol*. 2017;12:1788-1797.
2. Greenland S, Mansournia MA, Altman DG. Sparse data bias: a problem hiding in plain sight. *BMJ*. 2016;352:i1981.
3. Ayubi E, Safiri S. Bias in association between FEV1/FVC% predicted at 7 years and asthma-COPD overlap syndrome. *Am J Respir Crit Care Med*. 2017;196:115.
4. Ayubi E, Safiri S. Lateral lymph node recurrence after total thyroidectomy and central neck dissection in patients with papillary thyroid cancer without clinical evidence of lateral neck metastasis: Comment on data sparsity. *Oral Oncol*. 2017;69:128.
5. Steyerberg E. *Clinical Prediction Models: A Practical Approach to Development, Validation, And Updating*. Berlin, Germany: Springer Science and Business Media; 2008.

As they pointed out, the small number of cases of disease recurrence and death in our study may have resulted in imprecise confidence intervals (CIs), which may have slightly diminished the reliability of the identified indicators of poor prognosis. We are aware of these limitations and have addressed them in the “Discussion” section of our article.<sup>2</sup> We also think it meaningful that two factors—the presence of tumor spread through air spaces (STAS) and a short surgical clearance distance (<1 cm)—were statistically significant as poor prognostic factors despite the small numbers of recurrences and deaths in our study cohort. It is likely that this small number of events is the main cause of the imprecise CIs.

To calculate variance inflation factors (VIFs), we reexamined our sample data by using SPSS software (IBM Corp., Armonk, NY). For the four local recurrence factors that were significant in univariate analysis—tumor margin, STAS, age, and tumor grade—the VIFs were 1.011, 1.198, 1.071, and 1.249, respectively. The VIFs for locoregional recurrence factors were 1.237 for STAS; 1.621 for tumor grade; 1.072 for tumor size; and 1.461, 1.553, and 1.780 for lymph vessel, vascular, and pleural invasion, respectively. Finally, for distant recurrence factors, the VIFs were 1.231 for STAS, 1.076 for age; 1.635 for tumor grade; and 1.540, 1.786, and 1.455 for lymph vessel, vascular, and pleural invasion,