Letter to the Editor

Re: "Comparison of Treatment Strategies for Patients With Clinical Stage T1–3/N2 Lung Cancer"

Re: Cheng YF, Hung WH, Chen HC, et al. Comparison of Treatment Strategies for Patients With Clinical Stage T1–3/N2 Lung Cancer. *J Natl Compr Canc Netw* 2020;18(2):143–150.

We would like to comment on a recent article by Cheng et al¹ titled "Comparison of Treatment Strategies for Patients With Clinical Stage T1–3/N2 Lung Cancer." In this SEER-based work, the authors included patient diagnosed clinical stage T1–3/N2 lung cancer and compared the survival outcomes between patients receiving different treatment strategies. They found that in cT1–3N2 lung cancer, multimodal treatments tended to provide better 5-year overall survival than surgery alone or concurrent chemoradiotherapy.¹ However, the methodology they used in this study needs to be carefully evaluated.

First, in this study, the authors selected patients diagnosed with clinical stage T1–3N2M0 lung cancer between 2010 and 2015 as the training cohort. However, according to the SEER Program,² the "clinical stage" variable was not provided in the dataset until 2016. Therefore, for patients diagnosed before 2016, it was impossible for researchers to identify the clinical stage. Moreover, given that defining the clinical stage of patients is one of the focuses of this study, how the clinical stages of patients diagnosed between 2010 and 2015 were obtained requires detailed explanation.

Second, the definition of treatment strategies was questioned. In this study, regarding with the treatment groups, the authors classified the patients into 5 subgroups: surgery alone, surgery plus adjuvant chemotherapy with or without radiotherapy, neoadjuvant chemotherapy with or without radiotherapy plus surgery and adjuvant chemotherapy with or without radiotherapy, concurrent chemoradiotherapy, and chemotherapy and others. This seems very comprehensive, but it needs to be questioned in essence. In the SEER database, the sequence of radiotherapy and surgery could be obtained, but the record of the sequence of chemotherapy and the details of chemotherapy regimens was not provided.³ How the authors get the order of chemotherapy and radiotherapy and surgery is worth considering. Our views are derived from our practice in using the SEER database and are consistent with those of other SEER-based studies.^{4–6} Moreover, one recent publication reported that the SEER chemotherapy data had relatively low sensitivity. Therefore, the distinction between treatment models in this study is open to question.

In summary, although the research's intentions and results are good, the perspective of selecting patients and classification of the treatment methods needs further explanation.

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Letter to the Editor

Clinical Implications and Thoughts on Heterogeneous Treatment Strategies for Patients With Clinical Stage T1–3/N2 Lung Cancer

Re: Cheng YF, Hung WH, Chen HC, et al. Comparison of Treatment Strategies for Patients With Clinical Stage T1–3/N2 Lung Cancer. *J Natl Compr Canc Netw* 2020;18(2):143–150.

We would like to comment on the recent published article by Cheng et al¹ entitled "Comparison of Treatment Strategies for Patients With Clinical Stage T1–3/N2 Lung Cancer." Cheng et al compared the survival of patients with cT1–3N2 lung cancer who underwent different treatment strategies. They found that multimodal treatments tended to provide better 5-year overall survival than surgery alone or concurrent chemoradiotherapy, in which lobectomy was considered as the optimal

types of resection. However, we have some concerns.

First, as shown in Figure 2 and 3, there are intersections between Kaplan-Meier curves. For instance, therapy group 2 and 3 overlapped in Figure 2A–C, and pneumonectomy and lobectomy as well as others overlapped in Figure 3. Therefore, a time-dependent Cox regression model should have been used^{2,3} rather than the routine Cox proportional hazards regression model. The authors should clarify whether the results were changed in the time-dependent model.

Second, as shown in Figure 3, patients with cT2N2 or cT3N2 disease who underwent surgery accounted for a minority in

the entire cohort. Because the treatment strategies were heterogeneous (there were 5 different treatment modalities), it is obvious that different types of resection can hardly have comparability once subgroup analysis was made. In other words, the authors could not answer whether lobectomy was always the optimal choice for patients with lung cancer with the same clinical stage who underwent the same treatment modality. Additionally, there was no information concerning surgical margins and pulmonary function in the SEER database from 2010 through 2015,⁴ which is a major limitation to comparing surgery type in this study.

Lastly, the authors presented results of a multivariate analysis in Table 3, which

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included both surgery types and therapy groups. However, there could be collinearity between different surgical procedures and different treatment modality as covariates. For instance, for patients with cT1N2 lung cancer who underwent neoadjuvant chemoradiotherapy and experienced a complete response, sublobar resection may be performed; however, for those who did not undergo neoadjuvant therapy, lobectomy was routinely performed. The authors should address this issue to make readers better understand the results.

In summary, there are several inherent limitations of this study. The authors should make more explanation concerning the aforementioned problems.

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