Editorial

A national-scale lung cancer research targeting women who underwent surgery

Mariana Carolina Lopez-Pacheco[1,2], Su Ryon Shin[1]^, Dohun Kim[3]^

[1]Division of Engineering in Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA, USA; [2]Tecnológico de Monterrey, Escuela de Ingeniería y Ciencias, Campus Guadalajara, Jalisco, Mexico; [3]Department of Thoracic and Cardiovascular Surgery, College of Medicine, Chungbuk National University and Chungbuk National University Hospital, Cheongju, Korea

Correspondence to: Dohun Kim, MD, PhD. Department of Thoracic and Cardiovascular Surgery, College of Medicine, Chungbuk National University, 410 Sungbong-Ro, Heungduk-Gu, Cheongju 361-763, Korea. Email: mwille@chungbuk.ac.kr.

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The paper named "*The clinico-pathological characteristics of surgically treated young women with NSCLC*" is a large-scale study that analyzed 11,460 non-small cell lung cancer (NSCLC) patients from 2007 to 2020 (1). Only female patients who underwent surgery were targeted in the study cohort. A retrospective study method was adopted, the patients were separated into two groups, taking 55 years of age as the division point. Propensity score matching was performed in survival analysis. All the data used for this study was obtained from the Polish Lung Cancer Study Group.

Among the various facts claimed by the paper, the most noteworthy is the fact that young women under the age of 55 years have a higher risk of presenting advanced stage. The paper mentions two reasons for this (1). First, young women may tend to ignore symptoms because they are less prone to cancer, leading to late detection. Second, tumors of the younger patients might be more biologically aggressive, this would imply that the time from symptom detection to advanced-stage cancer is short when compared to older patients. In addition, since young patients show a similar mortality rate to that of the elderly despite having fewer underlying diseases, it is argued that proper management of female patients of all ages is necessary. This paper analyzed the differences in survival according to different age groups and the causes for only female lung cancer patients. However, there are some points that need to be carefully considered in the following points.

First, there are not enough information about the methods and criteria for patient selection. NSCLC was targeted in the study, but based on what is displayed on the table, only patients with lung adenocarcinoma (LUAD) and squamous cell carcinoma (SQC) were included. However, NSCLC also includes adenosquamous, large cell, and other diverse types of cells, which show different pathophysiologic features from LUAD or SQC (2,3). Detailed criteria for the cell type would be better for analyzing characteristics of the cohort. Next, no treatments other than surgery were not mentioned in the paper, although the authors commented that the study group was limited to patients who had undergone surgery. As referring the pathologic stages of the patients, it was highly probable that patients who received adjuvant or neoadjuvant therapy were included in the study group. Such information should be presented in the survival analysis because they had a meaningful impact on survival. If such patients were omitted, it could be problematic because it was a selection bias. Finally, patients with R1 resection (incomplete resection) and with incomplete follow-up

^ ORCID: Su Ryon Shin, 0000-0003-0864-6482; Dohun Kim, 0000-0001-8304-0232.

were excluded from the study, but the detailed information including proportion or number were not presented. The lack of such information makes it difficult to determine whether the patients were analyzed here are sufficiently representative of the entirety of the whole patients.

Second, grouping criteria for the patient. The authors defined that the age of 55 would be the criteria for the division of the different patient groups because it was the youngest age at which the sizes of the group were large enough to be compared statistically. However, because of this being a medical paper, biomedical evidence is required for classifying patients. According to other papers, there were specific criteria such as the frequency of diseases (e.g., asthma or chronic obstructive pulmonary disease), social transition (retirement age), or biological transformation (e.g., octogenarian) (4-6). The lack of biomedical evidence may function as a limitation for researchers who want to explain medical problems by referring to the results presented on this paper in the future.

Third, although it was mentioned above, information on treatment other than surgery is lacking. Lung cancer treatment does not consist of surgery alone (7,8). Considering that treatment other than surgery is required for stage II or higher, sometimes even including stage I, 48% in young and 45% in older patients included in this study require adjuvant therapy, and 12% (young) and 10% (older) require tri-modality (neoadjuvant-surgery-adjuvant) treatment (or definitive concurrent chemo-radio therapy or immune therapy without surgery) (7). If treatment other than surgery were omitted in patients presenting these conditions, there would be a possibility of medical malpractice. On the other hand, if there were patients who received treatment other than surgery, but such treatment history was not considered in the survival analysis, there would be a problem when interpreting the results.

Fourth, standardized mortality should be used to compare the survival of patients of different ages. For example, patients aged 75 years may die for various reasons other than lung cancer. However, death of patients under 55 is unlikely to occur unless there are specific reasons including cancers. Of course, no special manipulation is required to analyze the general mortality rate for each group, but since the lung cancer mortality rate is what should be analyzed here, it should not be disturbed by age. In other words, if mortality rates are simply compared without appropriate age correction, the mortality rates of the elderly may not be accurate since they would inevitably be significantly higher. According to this paper, there was difference in mortality between groups in stage IA2 (P=0.0037), but no difference in stage IA3 (P=0.11). Comparable results were also observed between stages IIIA and IIIB. In this study, no trend or pattern was observed according to the up staging. These irregularities can be modified by the adoption of standardized mortality rates. The expected outcome would be that the difference in mortality rate by age were remarkable in the lower pathologic stage but were not as the stage goes up. This would be because the advanced stages for lung cancer are known to be more powerful prognostic factors than age itself (6).

Fifth, a statistical problem was found. The authors applied the propensity scoring method (PSM) to fairly compare the survival of the two groups and eliminate confounding factors as much as possible (*Tab. 4* and *Fig. S1* in the paper) (1). However, since adjuvant or neoadjuvant therapy were not considered in PSM, it cannot be said that the two groups are not statistically different. Furthermore, when obtaining the prognosis factor through Cox proportional hazard regression, it is important to check for multicollinearity. Multicollinearity check is usually carried out to make sure that variables used in the analysis are independent from each other. Nonetheless, if there is a close relationship between the variables it can be considered a violation of collinearity, which would have implications in the analysis of the association between the variables and the results (9). In this case, although the authors proved that there is no violation by presenting the variance inflation factor (VIF), violation of multicollinearity is not determined by mathematical calculations alone. For example, stages are heavily influenced by the pathologic N (pN) descriptor. To name a few examples, pN0 is stage I, pN1 is stage II, and pN2 is most likely stage III. In other words, since pN and stage are deeply related, the probability of multicollinearity being violated is very high. In addition, the authors only used propensity score (PS)-matched patients for analysis. This means that, although all patients in the younger group were used in the analysis, only patients in the control group with a similar health status to the younger patients (i.e., older people who were healthier) were included, so it is hard to see that the study could represent the entire population. Considering these points, if Cox regression is corrected, it is thought that the results of this paper, which state that the risk is not different between pN0 and pN1 patients, will be different. Last, it is also regrettable that clear grounds for variable selection were not presented

during multivariate analysis.

Nevertheless, this paper is still important in the following respects. Since a large amount of data was obtained and analyzed from a nation-wide trust-worthy organization, this study can be used for similar studies. In addition, since the subject was limited to female patients who underwent surgery, an in-depth analysis of the relevant part can be expected. The smoking history of women has been decreasing, but it is still higher in Poland, which can lead to a higher incidence of lung cancer. In fact, no lung cancer except local one that requires operations increases, so it is timely to investigate surgery for female lung cancer patients (10). Furthermore, since the difference in the results of the treatments according to age was analyzed, it can be helpful to those who need to plan an anti-cancer policy. Lastly, based on this paper, research on cost appropriateness according to treatment method, usage patterns of medical institutions by region, population, and age and the resulting difference in clinical results as well as patient survival and life quality according to the latest treatment such as targeted/immunotherapy, etc. will also be able to proceed.

In conclusion, this paper is a study of lung cancer surgery that proves timely opinion with large-scale data. Care should be taken when interpreting the results in several points but it is suggested that researchers look into this paper to obtain information on this regard since this paper has a considerable contribution to be made through future research.

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Footnote

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References

1. Trojnar A, Domagała-Kulawik J, Sienkiewicz-Ulita A, et al. The clinico-pathological characteristics of surgically treated young women with NSCLC. Transl Lung Cancer Res 2022;11:2382-94.
2. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol 2015;10:1243-60.
3. Tsao MS, Nicholson AG, Maleszewski JJ, et al. Introduction to 2021 WHO Classification of Thoracic Tumors. J Thorac Oncol 2022;17:e1-4.
4. Kim D, Kim SY, Suh B, et al. Trend Analysis for the Choice and Cost of Lung Cancer Treatment in South Korea, 2003-2013. Cancer Res Treat 2018;50:757-67.
5. Nam SH, Kim KW, Kim SW, et al. Fate of spontaneous pneumothorax from middle to old age: how to overcome an irritating recurrence? J Thorac Dis 2019;11:4782-9.
6. Oxnard GR, Fidias P, Muzikansky A, et al. Non-small cell lung cancer in octogenarians: treatment practices and preferences. J Thorac Oncol 2007;2:1029-35.
7. Ettinger DS, Wood DE, Aisner DL, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 2.2021. J Natl Compr Canc Netw 2021;19:254-66.
8. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med 2022;386:1973-85.

9. Vatcheva KP, Lee M, McCormick JB, et al. Multicollinearity in Regression Analyses Conducted in Epidemiologic Studies. Epidemiology (Sunnyvale) 2016;6:227.
10. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7-33.

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