Title: A survival analysis using physique-adjusted tumor size of non-small cell lung cancer

Authors: Naoki Ozeki, MD [a], Takayuki Fukui, MD [a], Koji Kawaguchi, MD [a], Shota Nakamura, MD [a], Shuhei Hakiri, MD [a], Taketo Kato, MD [a], Akihiro Hirakawa, PhD [b], and Kohei Yokoi, MD [a]

Institutions:

[a] Department of Thoracic Surgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

[b] Statistical Analysis Section, Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

Corresponding author: Naoki Ozeki, Department of Thoracic Surgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

Tel: +81-52-744-2375; Fax: +81-52-744-2382

E-mail: naokiozeki@med.nagoya-u.ac.jp

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ABSTRACT

Background: The differences in individuals' body size have not been well considered when analyzing the survival of patients with non-small cell lung cancer (NSCLC). We hypothesized that physique-adjusted tumor size is superior to actual tumor size in predicting the prognosis. **Methods**: Eight hundred and forty-two patients who underwent R0 resection of NSCLC between 2005 and 2012 were retrospectively reviewed, and the overall survival (OS) was evaluated. The physique-adjusted tumor size was defined as follows: x-adjusted tumor size = tumor size × mean value of x / individual value of x (x = height, weight, body surface area [BSA], or body mass index [BMI]). Tumor size category was defined as ≤ 2 cm, 2-3 cm, 3-5 cm, 5-7 cm, and > 7 cm. The separation index (SEP), which is the weighted mean of the absolute value of estimated regression coefficients over the subgroups with respect to a reference group, was used to measure the separation of subgroups. **Results**: The mean values of height, weight, BSA, and BMI were 160.7 cm, 57.6 kg, 1.59 m^2, and 22.2 kg/m^2, respectively. The 5-year survival rates ranged from 88% to 59% in the non-adjusted tumor size model (SEP, 1.937), from 90% to 57% in the height-adjusted model (SEP, 2.236), from 91% to 52% in the weight-adjusted model (SEP, 2.146), from 90% to 56% in the BSA-adjusted model (SEP, 2.077), and from 91% to 51% in the BMI-adjusted model (SEP, 2.169). **Conclusions**: Physique-adjusted tumor size can separate the survival better than actual tumor size.

Introduction

The differences in individuals' body size have not been well considered when analyzing the survival of patients with malignant tumors. Among many physical parameters, body mass index (BMI) has received the most attention in survival analyses of solid tumors, including lung cancer, breast cancer, and colorectal cancer [1-6]. However, to date, no published study has conducted a survival analysis after lung cancer surgery using other physical parameters such as height, weight, and body surface area (BSA).

Our clinical question is simply whether there is any difference in the prognosis between smaller patients and larger ones with the same-sized non-small cell lung cancer (NSCLC) after surgical resection. Even if a small patient and a large patient have the same-sized lung cancer, the tumor itself would be relatively larger in the smaller patient. In this same vein, the prognosis of a 150 cm 55 kg patient with a 2.5-cm NSCLC might be similar to that of a 180 cm 66 kg patient with a 3-cm NSCLC.

We hypothesized that the physique-adjusted tumor size (described below) was a better prognostic factor for estimating the NSCLC prognosis than the non-adjusted tumor size. We therefore investigated the utility of the physique-adjusted tumor size and non-adjusted tumor size in predicting the prognosis using the data of 842 NSCLC patients who underwent surgical resection at a single institution in Japan.

Patients and methods

Patients

The study was conducted with the approval of the Institutional Review Board of Nagoya University Hospital. We extracted the patients from the medical records of patients who underwent R0 resection for pathological stage IA to IIIA NSCLC without preoperative therapy at Nagoya University Hospital between 2005 and 2012. As a result, 842 patients with full clinical information were enrolled in this study. Pathological tumor size after formalin fixation was evaluated as tumor size.

The physique-adjusted tumor size was defined as follows:

x-adjusted tumor size = tumor size × mean value of x / individual value of x (x = height, weight, BSA, or BMI)

sex-height-adjusted tumor size = tumor size × 152.4 (in females) or 164.8 (in males) / individual value of height

where the mean value was defined as the mean value of the current study cohort and BSA and BMI were defined as follows:

$$\text{BSA } (m^2) = \text{weight } (kg)^{0.425} \times \text{height } (cm)^{0.725} \times 0.007184$$

$$\text{BMI } (kg/m^2) = \text{weight } (kg) / [\text{height } (cm) \times 0.01]^2$$

The 7th edition of the tumor-node-metastasis (TNM) classification [7] was applied in this cohort. Thus, the tumor size categories were ≤ 2 cm, 2-3 cm, 3-5 cm, 5-7 cm, and > 7 cm. The pathological diagnosis of the tumor was made based on the definition of the World Health Organization classification [8].

Statistical analysis

Overall survival (OS) was defined as the time from surgery to death due to any cause. Disease free survival (DFS) was defined as the time from surgery to relapse or death due to any cause. The Kaplan-Meier method was used to estimate the OS, and the log-rank test was used to compare the survival curves. A univariate and multivariate Cox regression analysis was performed to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for OS. To evaluate the prognostic significance of each of the physical parameters, age, sex, smoking status, forced expiratory volume in one second ($FEV_{1.0}$), diffusing capacity of the lung for carbon monoxide (DL_{CO}), tumor size, pathological N status, and histological type were adjusted in the multivariate analysis. All of these covariates had been found to be significant prognostic factors for the OS in a univariate analysis ($p < 0.05$). The separation index (SEP) proposed by Sauerbrei et al. [9], which is the weighted mean of the absolute value of estimated regression coefficients over the subgroups with respect to a baseline reference group, was used to evaluate the degree of separation of the survival curves among the five groups determined on the basis of

tumor size and physique-adjusted tumor size. A higher SEP indicates a better degree of separation.

Statistical significance was defined as $p < 0.05$. All analyses were conducted using the JMP software program (version 13.0.0, SAS institute Inc., Cary, NC, USA) and the SAS software program (version 9.3; SAS Institute Inc.).

Results

Clinicopathological characteristics

The clinicopathological characteristics of the 842 patients enrolled are shown in Table 1. The mean values of height, weight, BSA, and BMI in the cohort were 160.7 cm, 57.6 kg, 1.59 m^2, and 22.2 kg/m^2, respectively. The mean age was 68.1 years. Five hundred sixty-two patients were male, and 596 had a smoking history. The mean and median tumor size were 3.0 cm and 2.6 cm, respectively. Sixty hundred and ninety-nine patients underwent major lung resection. The cohort consisted of 565 adenocarcinomas, 206 squamous cell carcinomas, and 71 other histological types. Three hundred and twenty-two tumors were classified as pathological stage IA disease, 266 as stage IB disease, 101 as stage IIA disease, 62 as stage IIB disease, and 91 as stage IIIA disease.

OS curves

The median follow-up period of all patients was 48 months. Figure 1 shows the OS curves classified by each of the physique-adjusted models. The number of patients classified in the ≤ 2 cm category of each of physique-adjusted tumor size models was smaller than that of the non-adjusted tumor size model. The 5-year survival rates of this category in each of the physique-adjusted tumor size models were higher than that of the non-adjusted tumor size model (90%-91% vs. 88%). In contrast, the number of patients classified in the > 7 cm category of each of

the physique-adjusted tumor size models was larger than that of the non-adjusted tumor size model. The 5-year survival rates of this category in each of the physique-adjusted tumor size models were lower than that of the non-adjusted tumor size model (51-57% vs. 59%) (Figure 1 and Table 2). Given these findings, the OS curves in each of the physique-adjusted tumor size models seemed to be better separated and extended than those in the non-adjusted tumor size model.

SEPs for the OS

Table 2 includes the summary of the HRs, 95% CI, regression coefficient, the SEPs, and the 5-year survival rates of the physique-adjusted and non-adjusted tumor size group models. The highest SEP of 2.236 was observed in the height-adjusted tumor size model, and the second highest SEP of 2.169 was observed in the BMI-adjusted tumor size model, while the lowest SEP of 1.937 was observed in the non-adjusted tumor size model. Generally, mean height is significantly different between males and females. Since mean height would strongly influence our height-adjusted model, an analysis using a sex-height-adjusted tumor size model was additionally performed. The SEP in the sex-height-adjusted tumor size model was slightly lower than that in the height-adjusted tumor size model (2.125 vs. 2.236, Table 2).

SEPs for the OS in 677 pN0 patients

After limiting the cohort to the 677 patients with pN0 NSCLC, the highest and lowest SEP were observed in the BMI-adjusted and non-adjusted tumor size model, respectively. The SEPs in the non-adjusted, height-adjusted, weight-adjusted, BSA-adjusted, BMI-adjusted, and sex-height-adjusted tumor size models were 1.646, 1.891, 1.947, 1.818, 2.035, and 1.780, respectively (Figure 2 and Table 3).

SEPs for the DFS

In all the 842 patients, the SEP for the DFS was similarly analyzed. The highest and lowest SEP were observed in the height-adjusted and non-adjusted tumor size model, respectively. The SEPs for the DFS in the non-adjusted, height-adjusted, weight-adjusted, BSA-adjusted, BMI-adjusted, and sex-height-adjusted tumor size models were 1.872, 2.065, 2.007, 1.943, 2.001, and 2.059, respectively.

SEPs for the DFS in 677 pN0 patients

Limiting to the 677 pN0 patients, the highest and lowest SEP for the DFS were observed in the BMI-adjusted and non-adjusted tumor size model, respectively. The SEPs for the DFS in the non-adjusted, height-adjusted, weight-adjusted, BSA-adjusted, BMI-adjusted, and sex-height-adjusted tumor size models were 1.562, 1.680, 1.820, 1.667, 1.846, and 1.677, respectively

HRs and 95% CIs of the physical parameters

Table 4 shows the results of the multivariable Cox regression analysis of height for the OS. After adjusting for the age, sex, smoking status, $FEV_{1.0}$, DL_{CO}, tumor size, pathological N status, and histological type, we found a significant inverse impact of height on survival. Table 5 shows the results of the multivariable Cox regression analysis of BMI. BMI also had a significant impact on the OS. Similarly, a 1-SD increase of weight (HR,0.75; 95% CI, 0.63-0.90; p = 0.0016) and a 1-SD increase of BSA (HR,0.71; 95% CI, 0.59-0.86; p = 0.0005) were found to have a significant impact on the OS.

Discussion

This study is an exploratory study designed to compare the survival of NSCLC patients using non-adjusted tumor size (actual tumor size) and physique-adjusted tumor size. The SEP is now recognized as the only surrogate parameter that evaluate the degree of separation of the survival curves. Each calculated SEP in the physique-adjusted tumor sizes (height-, weight-, BSA-, and BMI-adjusted) in NSCLC patients was superior to that of the non-adjusted tumor size (actual tumor size). Moreover, height, weight, BSA, and also BMI were found to be significant factors in the Cox multivariate regression analysis. these results suggest that our hypothesis might be correct: the physique-adjusted tumor size was a better prognostic factor for survival than the

non-adjusted tumor size. As previous studies have indicated, sex, DL_{CO}, tumor size, pathological N status were strong prognostic factors predicting the OS [10,11]. Physique-adjusted tumor size might also help contribute to the development of a future TNM staging system and/or international comparison.

The cell number and cell size of various organs is known to vary according to several parameters such as age, sex, weight, pathology or evolutionary adaptations. Taking this into consideration, in 2013, the total number of cells in the human body was estimated as 3.72×10^{13} for a 1.72m 70kg 30-year old adult based on bibliographical and/or mathematical approaches [12]. Since the physique-adjusted tumor size is based on the individual body size, it reflects the ratio of the number of lung cancer cells to the total number of cells in the body. Therefore, though this is only a hypothesis, our results suggest that the ratio of the number of lung cancer cells to the total number of cells in the body can be a superior prognostic factor than the number of lung cancer cells itself.

The association between height and lung cancer mortality has been examined epidemiologically in several studies [13-15]. In a meta-analysis with 1,085,949 participants (Asia: 7%; Europe: 60%; North America; 33%) in 121 studies, the HRs per 1-SD greater height were 0.97 (95% CI: 0.96–0.99) for death from any cause, 1.04 (1.03–1.06) for all cancer deaths, and 1.04 (1.02-1.06) for lung cancer deaths [13]. In another meta-analysis, with 408,381 Asian participants, the HRs for lung cancer death per 1-SD greater height were 1.13 (0.98-1.30) for

females and 1.09 (1.01-1.17) for males [14]. To our knowledge, however, no study has clarified the prognostic impact of height after lung cancer surgery, and the adjusted HRs per 1-SD greater height were 0.77 (0.62-0.96) in the present study. The reason for the discrepancy between our results after surgical resection and the previous epidemiological studies is to be mentioned. Because a larger person has a greater number of organ cells at risk of malignant transformation and/or proliferation, a larger body size has been proposed to be associated with a greater susceptibility to cancer [13]. However, when comparing people suffering from lung cancer, as we mentioned above, the better prognosis of a larger person might be due to the relatively smaller ratio of the number of lung cancer cell to the total number of cells in the lung and body.

Several reports regarding the association between BMI and lung cancer have been published previously [1-6]. Regarding surgical outcomes, Attaran et al. found that the survival rate of the group with BMI $\geq$ 30 was significantly higher after lung resection than among those with BMI < 30 [1]. Dhakal et al. found no marked difference regarding survival after lung resection between patients with BMI $\geq$ 25 and those with BMI < 25 [2]. We found a significantly better effect on survival in patients with a high BMI, as the HR per 1-SD increase in BMI was 0.82 (0.70-0.96) (Table 4). As previous studies have indicated, we think this was mainly because BMI is highly associated with the nutritional condition [1-6].

As a higher SEP indicates a better degree of separation, the height-adjusted tumor size separated the survival of NSCLC patients the best among the examined physical parameters.

However, it remained unclear why the SEP for the OS and DFS in the height-adjusted tumor size model was the highest among all of the models. One of the reasons might be that height is well acknowledged to have a significant correlation with lung volume (e.g. total lung capacity, vital capacity) [16] and also the number of cells in the lung. Nevertheless, because weight and BSA as well as height are highly associated with the total volume in the body and also the total number of cells in the body, we think all these parameters still have the potential to be interpreted as the best parameter for adjusting tumor size in the future. After limiting the cohort to the 677 patients with pN0 NSCLC, the SEP for the OS and DFS in the height-adjusted tumor size model was not the highest. In these circumstances, we regard it significant that each calculated SEP in the physique-adjusted tumor sizes was superior to that of the non-adjusted tumor size.

Several limitations associated with the present study warrant mention. First, this study was retrospective in nature. Second, because the original TNM classification is so well structured, the difference in the OS curves between the physique-adjusted tumor size models and the non-adjusted tumor size model was visually not very outstanding. Third, the follow-up period was relatively short. Forth, because the mean value of the physical parameters varies among countries and regions, it is necessary to modify the concept of physique-adjusted tumor size in international studies. Finally, as mentioned above, it remained unclear which physique-adjusted model is the best for adjusting tumor size.

Conclusions

This study only focused on the concept of adjusting tumor size using physical parameters. In conclusion, despite the fact that the current study included an exploratory challenge with several limitations, we believe it contains important information about tumor size from a unique perspective. The results suggest that physique-adjusted tumor size can separate the survival better than actual tumor size. Considering the differences among patients in physical parameters can be helpful in better understanding their prognosis.

Conflict of interest: The authors have declared that no conflict of interest exists.

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Figure Legends

Figure 1: The overall survival curves stratified by tumor size adjusted for physical parameters. (A) Non-adjusted tumor size model. (B) Height-adjusted tumor size model. (C) Weight-adjusted tumor size model. (D) Body surface area-adjusted tumor size model. (E) Body mass index-adjusted tumor size model. (F) Sex-height-adjusted tumor size model.

Figure 2: The overall survival curves in 677 pN0 patients stratified by tumor size adjusted for physical parameters. (A) Non-adjusted tumor size model. (B) Height-adjusted tumor size model. (C) Weight-adjusted tumor size model. (D) Body surface area-adjusted tumor size model. (E) Body mass index-adjusted tumor size model. (F) Sex-height-adjusted tumor size model.