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Clinical impact of lung age on postoperative complications and prognosis in patients aged > 60 years with non-small cell lung cancer and no comorbidities treated by anatomical resection

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ABSTRACT

Lung age formula proposed by Morris and Temple aimed to contribute toward smoking cessation programme and it was developed by Japanese Respiratory Society. It is considered as an important useful factor for predicting postoperative respiratory complications and survival in surgically treated patients with non small cell lung cancer. As the first for Turkish society, we aimed to evaluate clinical impact of lung age on postoperative complications in patients with NSCLC aged > 60 y. Survey included anatomically resected 80 NSCLC patients aged > 60 y in OMU Thoracic Surgery Clinic between years 2005 - 2015. Three groups were created using age groups <0, 0-10, >10, calculated as the difference between lung age and true age. Lung age was calculated according to Japanese Respiratory Society formula. Preoperative, intraoperative and postoperative prognostic factors were compared between three groups. Patient numbers in three groups were 18, 17 and 45. In preoperative factors gender, smoking, FEV1, FVC, SCC was related to lung age; postoperative respiratory complications and postoperative readmission related to respiratory complications were seen to have significant association with lung age. Lung age can be used as a clinical parameter to predict postoperative complication risk for NSCLC.

1. Introduction

Lung cancer (LC) is the most common cause of death from cancer worldwide (Morris and Temple, 1985). The number of patients with LC is relatively high due to long-term smoking, aging of the population, and various environmental factors. Smoking increases the descent velocity of forced expiratory volume in 1 second (FEV1).

Morris and Temple proposed a lung age formula to motivate smoking cessation, where smoking cessation has an important beneficial effect on pulmonary function (Morris and Temple, 1985). A lung age calculation was discussed at a meeting of Japanese Respiratory Society

(JRS) members in 2001, and lung age was calculated using a reverse equation created to imagine the reference value of forced expiratory volume in one second (Weinberger, 1992; Aizawa et al., 2007).

Yamaguchi et al. proposed alternative equations for calculating lung age based on a wider range of pulmonary function test values, to reduce error in lung age calculations (Yamaguchi et al., 2011).

Lung age can be easily understood by both clinicians and patients, and allows the difference between lung age and real age to be used for predicting pulmonary complications. However, there have been few reports regarding the usefulness of lung age in LC surgery.

2. Materials and methods

Ethical approval for this study was obtained from Ondokuz Mayis University (OMU) Medical Research Ethical Committee (Approval No. OMU KAEK 2015/475, issued December 24, 2015). The study population consisted of 80 patients aged > 60 years with stage 3a or lower non-small cell lung cancer (NSCLC), treated by anatomical resection at Ondokuz Mayis University Thoracic Surgery Service. The patients were divided into three groups according to the difference between lung age and chronological age: Group 1, age gap < 0 (n = 18); Group 2, age gap 0–10 years, n = 17; and Group 3, age gap > 10 years (n = 45). To evaluate the prognostic importance of lung age, patients with diabetes mellitus, chronic liver disease, renal insufficiency, serious arrhythmias, ischemic heart disease, collagen tissue disease, or non-pulmonary malignancies were excluded from the study.

The JRS formula, which has been widely adopted in clinical investigations, was applied to our population:

Males: lung age = 0.036 × height (cm) − 1.178 − FEV1 (L)/0.028

Females: lung age = 0.022 × height (cm) − 0.005 − FEV1 (L)/0.022

The prognostic value of lung age was compared among the three groups. The requirement for informed consent was waived due to the retrospective design of the study.

Statistical analyses were performed using SPSS for Windows software (Version 20.0; SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov and Shapiro–Wilk tests were used to evaluate the normality of the data distribution. Continuous and categorical variables were analyzed using Student's t test for comparison of two groups. Comparisons of more than two groups on categorical variables were performed using analysis of variance (ANOVA) and the Kruskal–Wallis H test. Associations between categorical variables were investigated with the Chi-square, N-Par, or Fisher's exact test. The survival data of the three groups were analyzed using the log-rank, Breslow, and Kaplan–Meier tests. In all analyses, p < 0.05 was taken to indicate statistical significance.

3. Results

The overall cohort comprised 6 (7.6%) females and 73 (92.4%) males. Group 1 was composed of 5 (29.4%) females and 12 (70.6%) males. Group 2 was composed of 1 female (70.6%) and 16 (94.1%) males. All 45 (100%) of the patients in Group 3 were male. Larger age gaps were associated with a significant decrease in the proportion of females and a significant increase in the proportion of males (p = 0.000).

The average chronological age was 67.1 years in Group 1, 66.4 years in Group 2, and 66.7 years in Group 3. There was no significant association between lung age and chronological age (p = 0.934). The average lung age was 62.1 years in Group 1, 71.7 years in Group 2, and 86.9 years in Group 3. Lung age increased significantly with increasing age gap (p = 0.000), while no significant association was observed with chronological age or age gap.

Number of smokers, FEV1, and percentage forced vital capacity (%FVC) were compared among the age gap groups. The average FEV1 was 54.42% in Group 1, 56.35% in Group 2, and 28.94% in Group 3. The average %FVC was 38.89% in Group 1, 40.41% in Group 2, and 41.18% in Group 3. The average of FVC was 49.94 in Group 1, 49.24 in Group 2, and 33.42 in Group 3. The

Table 1. Distribution of histologic subtypes among groups.

			Groups			Total
			x<=0	0<x<=10	x>10	x<=0
Histology	Adenocancer	Number	10	4	15	29
		% in Group	55.6%	23.5%	33.3%	36.3%
	Squamous cell cancer		6	9	25	40
		% in Group	33.3%	52.9%	55.6%	50.0%
	Large cell NE tumor		0	0	2	2
		% in Group	0%	0%	4.4%	2.5%
	Adenosquamous cell cancer		0	1	3	4
		% in Group	0%	5.9%	6.7%	5.0%
	Bronchoalveoler cancer		0	2	0	2
		% in Group	0%	11.8%	0%	2.5%
	Less differentiated cancer		1	0	0	1
		% in Group	5.6%	0%	0%	1.3%
	Sarcomatoid cancer		1	0	0	1
		% in Group	5.6%	0%	0%	1.3%
	Inflammatory pseudotumor		0	1	0	1
		% in Group	0%	5.9%	0%	1.3%
Total			18	17	45	80
		% Group	100%	100.0%	100.0%	100.0%

average of number of smokers was 24.92 in Group 1, 41.44 in Group 2, and 45.52 in Group 3. Smoking was significantly associated with lung age (p = 0.005). FEV1 and FVC decreased significantly with increasing average lung age (p = 0.000 and p = 0.008, respectively). There was no significant association between lung age and %FVC (p = 0.939).

The distribution of histopathological subtypes among the groups is illustrated in Table 1.

As the age gap increased, the rate of squamous cell cancer (SCC) diagnosis increased significantly, while that of adenocarcinoma diagnosis decreased significantly (p = 0.037). Large cell neuroendocrine (NE) tumor diagnosis was not associated with age gap.

The association of age gap with disease stage was also investigated. Stage 1a was seen in 11.1% (n = 2) of Group 1 patients, 23.5% (n = 4) of Group 2 patients, and 17.8% (n = 8) of Group 3 patients. Stage 1b was seen in 44.4% (n = 8) of Group 1 patients, 35.3% (n = 6) of Group 2 patients, and 26.7% (n = 12) of Group 3 patients. Stage 2a was seen in 16.7% (n = 3) of Group 1 patients, 5.9% (n = 1) of Group 2 patients, and 11.1% (n = 5) of Group 3 patients. Stage 2b was seen in 11.1% (n = 2) of Group 1 patients, 23.5% (n = 4) of Group 2 patients, and 26.7% (n = 12) of Group 3 patients. Stage 3a was in 16.7% (n = 3) of Group 1 patients, 11.8% (n = 2) of Group 2 patients, and 17.8% (n = 8) of Group 3 patients. Disease stage was not significantly related to age gap in the present study (p = 0.794).

In our analyses, although the increases in lung age and resection volume were directly proportional, the association was not statistically significant (p = 0.336) (Table 2).

Table 2. Distribution of resection volume among groups.

		Groups			Total
		x<=0	0<x<=10	x>10	x<=0
Lobectomy	Number	11	13	25	49
	% in Group	64.7%	76.5%	55.6%	62.0%
Bilobectomy	Number	2	1	8	11
	% in Group	11.8%	5.9%	17.8%	13.9%
Pneumonectomy	Number	3	3	10	16
	% in Group	17.6%	17.6%	22.2%	20.3%
Segmentectomy	Number	1	0	2	3
	% in Group	5.9%	0%	4.4%	3.8%
Total	Number	18	17	45	80
	% in Group	100.0%	100.0%	100.0%	100.0%

The associations of duration of operation, duration of drain withdrawal, and duration of hospitalization with lung age were investigated. Neither duration of operation nor duration of drain withdrawal showed a significant association with lung age (p = 0.608 and p = 0.708, respectively). The duration of hospitalization increased with increasing lung age, but the association was not statistically significant (p = 0.522).

The rate of postoperative intensive care unit (ICU) hospitalization for 1 day was 100% (n = 9) in Group 1, 100% (n = 9) in Group 2, and 84.2% (n = 16) in Group 3. The rate of postoperative ICU hospitalization for 2 days was 0% in Groups 1 and 2 and 10.5% (n = 2) in Group 3. No patients in Group 1 or 2 were hospitalized in the ICU within 3 days postoperatively, while the rate in Group 3 was 5.3% (n = 1). As age gap increased, the rate of postoperative ICU hospitalization also increased, but not statistically significantly (p = 0.129).

Postoperative intubation was performed in 46.2% (n = 6) of patients in Group 1, 0% (n = 0) in Group 2, and 53.8% (n = 7) in Group 3. Postoperative extubation was performed in 18% (n = 11) of patients in Group 1, 26.2% (n = 16) in Group 2, and 55.7% (n = 34) in Group 3. The association between age gap and postoperative intubation status was significant (p = 0.029).

There was a significant association between the rate of postoperative respiratory complications and age gap (p = 0.013) (Table 3).

Table 3. Distribution of histologic subtypes among groups.

			Groups			Total
			x<=0	0<x<=10	x>10	x<=0
Respiratory Complications	Expansion defect	Number	0	1	6	7
		% in Total	0%	14.3%	85.7%	100.0%
	Prolonged air leak	Number	4	2	6	12
		% in Total	33.3%	16.7%	50.0%	100.0%
	Dyspnea	Number	0	1	0	1
		% in Total	0%	100.0%	0%	100.0%
	Bronchopleural fistula	Number	0	1	0	1
		% in Total	0%	100.0%	0%	100.0%
	Recycling in sputum	Number	0	0	2	2
		% in Total	0%	0%	100.0%	100.0%
	Subcutaneous empysema	Number	0	0	1	1
		% in Total	0%	0%	100.0%	100.0%
	Respiratory arrest	Number	0	0	1	1
		% in Total	0%	0%	100.0%	100.0%
	Empyema	Number	0	1	0	1
		% in Total	0%	100.0%	0%	100.0%
	Haemorragic drainage	Number	0	1	0	1
		% in Total	0%	100.0%	0%	100.0%
Total		% in Total	14.8%	25.9%	59.3%	100.0%

Postoperative pleurodesis was performed in 7.7% (n = 1) of patients in Group 1, 0% (n = 0) in Group 2, and 23.1% (n = 3) in Group 3. Pleural aspiration was applied in 7.7% (n = 1) patients in Group 1, 15.4% (n = 15.4) in Group 2, and 30.8% (n = 4) in Group 3. The Heimlich valve was used in 7.7% (n = 1) of patients in Group 1, 0% (n = 0) in Group 2, and 7.7% (n = 19) in Group 3. As the age gap increased, so too did the rates of postoperative pleurodesis, pleural aspiration and Heimlich valve use (p = 0.092).

Postoperative nonpulmonary complications (cardiac arrhythmia, hypertension, ischemic heart disease), infection (wound infection), neurological sequelae (delirium), and urological symptoms (hematuria) were observed in 22.2% (n = 6) of patients in Group 1, 25.9% (n = 7) in Group 2, and 51.9% (n = 14) in Group 3. The rates of postoperative nonpulmonary complications increased with increasing age gap although the association was not statistically significant (p = 0.649). Readmission to hospital with pulmonary pathology was significantly associated with age gap (p = 0.022) (Table 4).

Table 4. Distribution of readmission to hospital with respiratory complications.

		Groups			Total
		x<=0	0<x<=10	x>10	x<=0
Readmission to hospital with respiratory complications					
Pneumonia	Number	1	1	2	4
	% in Groups	5.9%	5.9%	4.5%	5.1%
Dyspnea	Number	1	0	2	3
	% in Groups	5.9%	0%	4.5%	3.8%
Pleural effusion	Number	0	1	0	1
	% in Groups	0%	5.9%	0%	1.3%
Bronchopleural fistula	Number	0	0	3	3
	% in Groups	0%	0%	6.8%	3.8%
Empyema	Number	0	0	2	2
	% in Groups	0%	0%	4.5%	2.6%
Lung abscess	Number	0	0	1	1
	% in Groups	0%	0%	2.3%	1.3%
Pulmonary thromboembolism	Number	1	0	0	1
	% in Groups	5.9%	0%	0%	1.3%
Total	Number	18	17	45	80
	% in Groups	100.0%	100.0%	100.0%	100.0%

The rates of readmission to hospital with nonpulmonary pathology (cardiac arrhythmia, hypertension, ischemic heart disease), infection (wound infection), neurological sequelae (delirium), and urological symptoms (hematuria) were 41.2% (n = 7) in Group 1, 35.3% (n = 6) in Group 2, and 27.2% (n = 12) in Group 3. There was no significant association between lung age and readmission to hospital with nonpulmonary etiology (p = 0.727).

The association between postoperative survival and lung age was evaluated as shown in Figure 1. Postoperative survival decreased with increasing age gap, but the association was not statistically significant (p = 0.253).

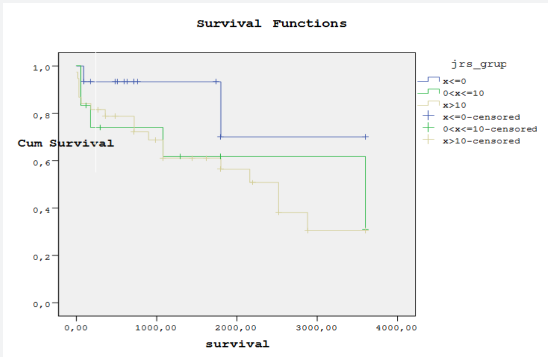

Fig. 1. Analyses of postoperative survival among groups.

4. Discussion

Surgery is the best treatment modality for early phase NSCLC, but postoperative morbidity and mortality are major problems for thoracic surgeons especially after surgical resection of NSCLC patients with chronic obstructive pulmonary disease (COPD). Evaluation of surgical prognosis requires knowledge of preoperative risk factors and postoperative morbidity and mortality rates. To evaluate lung function, the concept of lung age can be applied, where a lung age older than the chronological age indicates weak lung function.

In our study, we grouped the patients according to lung age and age gap (between lung and chronological age), because lung age can increase with the decreases in FEV1 seen with increasing chronological age. The age gap can also be applied as a standardized measurement to any age group, as demonstrated in the literature (Ogawa et al., 2014).

The JRS formula, which has been adopted in many clinical investigations, was used in our study. Similar to previous reports, there was a significant increase in the proportion of male patients with increasing age gap. In the present study, lung age also increased significantly with increasing age gap, similar to previous reports. However, in contrast to the literature, chronological age and age gap did not show a significant association in the present study (Ogawa et al., 2014).

As in previous studies, smoking was significantly related to age gap in the present study, with smokers showing a markedly advanced lung age compared to chronological age (Haruki et al., 2010; Ogawa et al., 2014). In our study, FEV1 and FVC decreased significantly with increasing lung age, but %FVC and lung age did not show a significant association. Ogawa et al. reported that lung age decreased as FEV1 increased, but not statistically significantly (Ogawa et al., 2014). To our knowledge, there have been no other studies regarding the relations of lung age with FVC and %FVC.

In the present study, the rate of SCC diagnosis increased significantly, while the rate of adenocarcinoma diagnosis decreased significantly, with increasing age gap. In addition, NE tumor diagnosis was not significantly associated with age gap, as in previous reports.

Similar to previous reports, age gap and disease stage did not show a significant association in the present study; Ogawa et al. reported that increases in lung age and disease stage were directly proportional (Haruki et al., 2010; Ogawa et al., 2014). As in the present study, increased lung age and resection volume were reported previously to be associated, although the relationship was not statistically significant (Haruki et al., 2010; Ogawa et al., 2014).

There was no significant association of duration of operation with lung age, or of duration of chest tube withdrawal with lung age, in our study or in the literature (Ogawa et al., 2014). Previously, the duration of hospitalization was reported to increase with increasing lung age (Ogawa et al., 2014), while in the present study that association was not statistically significant.

In the present study, length of ICU stay also increased with increasing lung age, but this relationship was not statistically significant. Postoperative respiratory complications were significantly associated with lung age, as reported previously (Ogawa et al., 2014). The rate of pleural adhesion also increased with increasing age gap, but this relationship was not statistically significant.

Similarly, it was reported that nonrespiratory complications also increased with increasing lung age (Ogawa et al., 2014). Readmission to hospital with respiratory and nonrespiratory complications also increased with increasing age gap in the present study, similar to the report by Ogawa et al. (2014).

Preoperative pulmonary physiotherapy, preoperative bronchodilator therapy, effective bronchial lavage, smoking cessation programs, etc., can markedly reduce rates of postoperative readmission to hospital. Especially in NSCLC patients aged > 60 years (particularly those with COPD), lung age should be calculated to predict the likelihood of postoperative complications and enhance prognostic accuracy.

In the present study, patients with an age gap > 10 years showed significantly increased rates of postoperative complications and readmission to hospital; thus, special attention should be paid to such patients.

Although lung age is a simple and effective way to determine patient status, the calculation thereof is prone to error. FEV1 can decrease in nonsmoking patients with asthma, pulmonary fibrosis, obesity, or neuromuscular disease, and it is unclear how best to determine the lung age in such patients. This is because it remains unclear how to measure the effects of factors other than smoking on a smoker's lung age where, if the FEV1 cannot be evaluated accurately, estimated lung age will be prone to error.

This study had some limitations. First, it used a retrospective design, and 32.5% of the patients died due to recurrent cancer or other diseases. Thus, prospective data are needed to support our findings. Further studies aimed at predicting long-term outcomes using regression equations specific to the Turkish population are also necessary. Nevertheless, our study suggests a model for predicting postoperative complications in older patients with NSCLC.

The age gap between chronological age and lung age was significantly associated with postoperative complications in univariate analysis, and was shown to be an independent predictor of complications in multivariate analysis. Lung age should be investigated in more detail as a potential predictor of both postoperative complications and prognosis. This parameter could help both patients and clinicians to gain a better understanding of pulmonary function.

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