Objective: There are still controversies about the surgical benefits for elderly lung cancer. The aims of this study were to assess impacts of aging for non-small cell lung cancer (NSCLC) following pulmonary resection.

Methods: A retrospective study was undertaken for patients operated at a curative intent from January 1998 to October 2008. Patients were divided into two groups: Group 1 consisted of patients aged at least 75 years old, and group 2 were patients less than 75 years old. Perioperative characteristics and details, hospital courses, surgery-related morbidities, surgical mortality, and survival were compared between groups.

Results: Of 442 eligible patients, 73 patients (16.5%) were in group 1 (mean age 78.3 years) and 369 (83.5%) patients were in group 2 (mean age 62.5 years). The following data were compared with statistical significance: hospital stay (17.8 vs. 8.9 days), mortality rate (8.2 vs. 2.2%), morbidity rate (26.0 vs. 13.3%), and length in intensive care unit (5.7 vs. 3.2 days). The main causes for morbidities in group 1 showed cardiopulmonary-related. Tumor stage without considering age had statistically significant influence on survival. Survivals of two groups were comparative. (p = 0.10) Intriguingly, the disease-related survival (28.3 months; p = 0.008) and progression-free survival (25.0 months; p < 0.001) in group 1 were significantly better than group 2 (20.2 and 12.2 months).

Conclusions: Although operation for NSCLC in the elderly patients causes more complications, especially in the cardiopulmonary system, their outcome showed better than their younger counterparts. Pulmonary resection for elderly patients may get longer disease control. Elderly patients with physical fit for surgery should not be considered as a contraindication to pulmonary resection based on age alone.

Keywords: lung cancer, elderly, surgery, survival, disease control

Introduction

Both human life expectancy and the amount of aged population are gradually increasing along with civilization. At the same time, both eastern and western epidemiological studies show increased incidence of lung cancer in elderly patients.1–4) Given that more than 50% of lung cancer patients are diagnosed over the age of 65 and about 30% over the age of 70, lung cancer has become the disease of aged people.5,6)
Surgery for Elderly Lung Cancer

Aging is a slow process along with decline in physiological functions and decrease in functional reserve, causing recovery from a major stress, such as surgery, not as quick as the younger.\textsuperscript{7} No established cut-off age related to pulmonary surgery was set before, but several reports had discussed the impact of major surgery and critical diseases to different age cohorts, namely, young-old (65–74), old-old (75–84) and oldest-old (≥85).\textsuperscript{8–11} Among them, stress buffering properties of physiological support in old-old and oldest-old patients (≥75) were considered especially evident. Thus age 75 years was commonly accepted as critical cut-off point for pulmonary resection.\textsuperscript{11–13}

Along with aging population, increasing numbers of elderly patients with lung cancer led to significant growth in the demand of surgical intervention for the elderly.\textsuperscript{1,14,15} Thus, in this study, we retrospectively collected patients with non-small cell lung cancer (NSCLC) and receiving curative resection to analyze the outcomes of treatment in the elderly and to determine the impacts of age on survival.

Methods

Eligible patients with operated NSCLC, clinically less than stage 2 and equivocal stage 3A, were enrolled between January 1998 and October 2008. Clinical data of patients were retrospectively analyzed. Patients were divided into two groups: group 1 is the elderly patients aged at least 75 years old; group 2 consisted of non-elderly patients aged less than 75 years old. All patients underwent curative pulmonary resection for their primary NSCLC. The degree of resections for the tumors includes extended resection, pneumonectomy, lobectomy, or bilobectomy, and limited (or sublobar) resection, anatomical segmentectomy or partial resection. The decisions for the types of resection were complex, but could be summarized as according to the patient performance, tumor status, cardiopulmonary function, and tumor location. Tumor TNM staging was reviewed according to AJCC staging manual, 6th edition because most patients were treated during the 6th edition time. Peri-operative variables between two groups were compared. This study was approved by the institutional review board of the hospital. (Protocol number: 09MH1S040).

Preoperative evaluation included detailed risk assessment based on history of cardiopulmonary, cerebrovascular, hepatic and renal disease. All patients before operations had been checked with chest roentgenography, bronchoscopy, abdominal sonography (AS), cell and biochemistry profile, electrocardiography (EKG), pulmonary functional tests with spirometry and arterial blood gas analysis, and computer tomography (CT) or optionally, whole body positron emission tomography (WBPET). Following pulmonary resection, patients were followed up every one to two months and systemically checked every 3 months for first two years and then every 6 months thereafter. The postoperative systemic check included chest roentgenography, CT, AS, serum levels of carcinoembryonic antigen (for adenocarcinoma) and squamous cell carcinoma (for squamous cell carcinoma), Tc-m99 whole body bone scan, and brain scan or optionally, WBPET.

For locally advanced or recurrent NSCLC after operations, eligible patients received chemotherapy and/or radiotherapy, concurrent or sequential, according to their performance and tumor status. After recurrence, the patients received salvage therapy as indicated. The regimens for chemotherapy included platinum, fluorouracil, gemcitabine, navelbine, taxanes, epirubicin, pemetrexed, tyrosine kinase inhibitors (gefitinib and erlotinib) and bevacizumab.

For accurate comparisons of stages and survival outcomes, patients who received surgery with incomplete resection, macroscopically or microscopically, and with preoperative chemotherapy and/or radiotherapy, were excluded in this study. Survivals were calculated from the date of surgery to the most recent follow-up contact or to the date of death. Statistical analyses were performed with the independent \( t \)-test and the chi-square test or fisher’s exact test for continuous and categorical variables, respectively. Data were collected from medical records and personal interview. For survival analysis, Kaplan-Meier method was used and compared with log-rank test by using the SPSS/PC+ Advanced Statistics 12.0 software package (SPSS Inc., Chicago, Illinois, USA). Difference was considered significant when the \( p \) value was less than 0.05.

Results

There were 3721 patients diagnosed and treated for NSCLC in our database. Of them, 442 (11.9\%) patients following pulmonary resection were enrolled for studies about comparative impacts of age on outcome. There were 73 patients in the group 1 and 369 patients in the group 2. The mean age of enrolled patients was 64.5 years (range from 31 to 94 years), 78.3 years for group 1 and 62.5 years for group 2. Their demographics and
perioperative characteristics are shown in Table 1. The histological types and staging distribution showed no difference between groups, indicating homogeneity of the groups. However, elderly patients tended to have worse performance status and received less extended operation and more minimal invasive surgery than their younger controls although there were no significant differences. The postoperative hospital stay, morbidity and mortality rates, and length in intensive care unit (ICU) in group 1 were significantly greater than group 2. (Table 2) Cardiopulmonary-related complications were the main causes of perioperative morbidities. Besides, there was no operation-related mortality for thoracoscopic surgery in both groups.

Under tolerance consideration, older patients after pulmonary resection received much less chemotherapy and/or radiotherapy than their younger controls. \( p = 0.002 \) There were also no significant benefits from chemotherapy and/or radiotherapy for patients following pulmonary resection in this study.

Tumor stages showed significant influences on survival. (Fig. 1) The median overall survivals (OS) of two groups (25.4 vs. 20.2 months; 95% confidence interval [CI], 24.1 to 27.4 months vs. 16.1 to 24.2 months) were comparative. \( p = 0.10 \) Intriguingly, the disease-related survival (DRS) was significantly better in elderly group (28.3 vs. 20.2 months; 95% CI, 16.3 to 39.4 months vs. 16.2 to 24.3 months) than their younger control. (Fig. 2) Analysis of progression-free survival (PFS) showed with a similar result. Median time-to-progression (TTP) was 25.0 months (95% CI, 17.8 to 32.3 months) for group 1 and 12.2 months (95% CI, 9.2 to 15.3 months) for group 2 \( p < 0.001 \).

**Discussion**

This study presents that, compared to their younger counterparts, elderly patients with NSCLC following
treatment of choices for early or local NSCLC. 16) However, the operation rate for elderly patients (4.9%) is much lower than their younger controls (17.7%) in this study. There should be many factors involved in the operation of elderly lung cancer which created complex obstacles to surgery of the elderly patients.

The rates of surgical morbidity and mortality for operated elderly lung cancers showed significantly higher than their younger controls in this study. Elderly patients usually had poorly medical and physiological status. 17–18) Differences in surgical morbidity and mortality for elderly patients might be due of increased incidence of coexisting cardiopulmonary or cerebrovascular diseases 19–21) and resultant compromised pulmonary and cardiovascular function. 1) Age-related deterioration of pulmonary function does not usually produce symptoms in unstressed individuals. However, in response to stress and surgery, reduction in compliance of respiratory vital capacity and maximum voluntary ventilation becomes evident. 7) The physiological reservoirs of respiratory responses to peri-operative and post-operative hypoxia and hypercapnea are also markedly diminished. 22,23) Consequently, these factors render operated elderly patients with higher complications and mortality rate.

Along with aging, physiological function of both pulmonary resection would get better tumor control for longer PFS and DRS and comparable OS even though surgery results higher morbidity rate. The data indicates that age may have suspected effects on tumor growth. Curative resection is commonly accepted as the best surgery for Elderly Lung Cancer

### Table 2 Treatment results of patients with non-small cell lung cancer

<table>
<thead>
<tr>
<th>Complications/Groups</th>
<th>Non-elderly (N = 369)</th>
<th>Elderly (N = 73)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-OP stay (days)</td>
<td>8.9 ± 6.7</td>
<td>17.8 ± 3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>3.2 ± 1.1</td>
<td>5.7 ± 3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality—no. (%)</td>
<td>8 (2.2)</td>
<td>6 (8.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Morbidities—no. (%)</td>
<td>49 (13.3)</td>
<td>19 (26.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td>32</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>21</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>15</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>ARDS</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>AMI</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>29</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Prolonged air leak (≥5days)</td>
<td>24 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Wound infection</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CVA</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lobar torsion</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Empyema</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Postoperative bleeding</td>
<td>1 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>others</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Multiple complex complications were found on several patients. Post-OP: postoperative; ICU: intensive care unit; NS: no significance; ARDS: adult respiratory distress syndrome; AMI: acute myocardial infarction; CVA: cerebrovascular accident.

![Fig. 1 Survival for different stages of operated patients without considering age. CIS: carcinoma in situ](image)
Therefore, operated elderly patients should need detailed preoperative assessment, effective perioperative control of coexisting diseases and hemodynamics, and intensive postoperative monitoring and care.

Cancers are immunogenic and the immune system can and does protect against tumorigenesis. Several investigations had ever reported that older people were more likely to develop cancer and age may change tumor growth and spreading. Because age changes immunity of aged people, age contributes to the increased incidence and mortality of most cancers. In conformity with the previous reports, the OS of current study showed comparable between elderly patients and their younger counterparts. On the other hand, the PFS and DRS in the elderly group showed longer than their younger counterparts. This result seems to reflect the report by Weksler, et al.: aging slows tumor growth, decreases metastasis, and increases survival. A recent report by Ohtani, et al. also suggested that the role of cellular senescence in aging is important as a potent mechanism for tumor suppression and protection. Age should not be an only absolutely provocative factor to tumorigenesis, but age may have adverse effect on the tumor growth. However, the relationship between cancer and aging is too complicated to be concluded from current studies. There is still uncertain regarding to the growth and metastasis of cancer in elderly patients. The variant factors would include exposure to carcinogens and changes in the host defense during aging. There should be further studied for the relationship of aging and carcinogenesis.

The average life expectancy of patients with untreated or palliated early-stage NSCLC is 1.65 years. Given that the average life expectancy of a person at 75 years of age exceeds 8 years, life limiting factor for patients with early stage lung cancer at the age of 75 years or even older may not be their age, but, instead, the cancer status. Several studies had ever demonstrated benefits of active therapy in elderly population and comparable results between two cohort patients. However, on the other hand, published evidences showed that elderly patients were regarded not a potentially beneficial group because of chronological age and many treatments withhold due of their physiological considerations. Reluctance to treat and fear for treatment toxicity for even fit elderly patients had been presented for the main causes for comparable or poor overall results of them. The phenomenon seemed to be reproducibly disclosed in this study: although surgical treatment can not get significant better OS in the elderly group than the younger control,

sympathetic and parasympathetic nervous systems gradually decreases. Effect of impaired autonomic activity may induce impaired thermoregulation in response to stress. During anesthesia, older patients cool to a greater extent and require a longer period of time for rewarming. The adverse effects of hypothermia may result in increased postoperative discomfort, a longer duration of hospital stay and predisposition to perioperative wound infection and morbid cardiac events. Such influences reflect in the elderly patients to be both ICU stay and postoperative hospital stay longer than their younger controls.

Fig. 2 (a) Disease-related survival ($P = 0.008$) and (b) progression-free survival ($P < 0.001$) for different age group of patients with lung cancer showed statistically significant difference.
the benefits were reflected in PFS. Thus, aggressive
treatment for lung cancer in the aged group should be
legitimately considered if it can be performed with care-
ful pretreatment assessment. Although elderly patients
have more underlying comorbidities than younger dupli-
cates and increased risks associated with surgery from
15.3% to 58%, chronicologic age alone should not be con-
considered as an absolute contraindication for pulmo-
ny resection. Therefore, pulmonary oncologists
should be aware of the heterogeneity of the elderly
patients and the importance of an individualized compre-
prehensive assessment for these special patients. Besides,
even with more complicated physiological dysfunction,
comprehensive treatments such as anatomically sublobar
resection through minimal invasive surgery should be
another option of treatment which had been demon-
strated with substantially reduction of morbidity and
mortality for elderly patients with lung cancer.

Current study was a retrospective case. There were
some limitations for this study such as different patients
risk for the age cohorts, surgical selection of the cases,
mismatched patient distribution between groups, and
mixed treatments. Besides, the improvement of chemo-
therapeutic agents and treatment concepts for lung cancer
in clinical practice, such as targeting therapy and staging
system, were progress, especially favoring priority in
elderly patients, during the study period. However, the
valuable findings of this study were the intrigue results
about the stressful influences of age on surgical recovery
and the possible change of tumor growth by age even
though the limitations of the study warranted further
detailed study.

In conclusion, although elderly patients with NSCLC
following surgery may have more complications than
younger patients, chronicologic age only should not be con-
sidered as the exclusive indicator for pulmonary surgery
in elderly patients. Medically fit elderly patients would
warrant for curative resection for better disease control.
Preoperative assessment of elderly patients would be
emphasized on cardiopulmonary function in order to
reduce the postoperative morbidity and mortality.

Disclosure Statement

There are none of authors with disclosure of conflict of
interest in this article.

References

1) Owonikoko TK, Ragin CC, Belani CP, et al. Lung can-
cer in elderly patients: an analysis of the surveillance,
epidemiology, and end results database. J Clin Oncol
world cancer burden: Globocan 2000. Int J Cancer
3) Mun M, Kohno T. Video-assisted thoracic surgery
for clinical stage I lung cancer in octogenarians. Ann
4) Cattaneo SM, Park BJ, Wilton AS, et al. Use of
video-assisted thoracic surgery for lobectomy in the
elderly results in fewer complications. Ann Thorac
5) Gridelli C, Aapro M, Ardizzoni A, et al. Treatment of
advanced non-small-cell lung cancer in the elderly:
results of an international expert panel. J Clin Oncol
6) Gridelli C, Perrone F, Monfardini S. Lung cancer in
7) Cheng SP, Yang TL, Jeng KS. Perioperative care of the
of age and coronary artery disease on homocysteine
levels in the young old compared with the old old and
of social network characteristics to 5-year mortality
among young-old versus old-old white women in an
10) Chalfin DB, Carlon GC. Age and utilization of inten-
sive care unit resources of critically ill cancer patients.
11) Rueth NM, Parsons HM, Habermann EB, et al. Surgi-
cal treatment of lung cancer: predicting postoperative
morbidity in the elderly population. J Thorac Cardio-
vasc Surg 2012; 143: 1314-23.
12) Schneider T, Pfannschmidt J, Muley T, et al. A retro-
spective analysis of short and long-term survival after
curative pulmonary resection for lung cancer in elderly
non-small cell lung cancer (NSCLC) in patients aged
75 years and older: does age determine survival after
14) Brown JS, Erat D, Trask C, et al. Age and the treat-
population and its impact on the surgery workforce.
16) Bölükbas S, Beqiri S, Bergmann T, et al. Pulmo-
mary resection of non-small cell lung cancer: is sur-
vival in the elderly not affected by tumor stage after
complete resection? Thorac Cardiovasc Surg 2008;
56: 476-81.