Aim of the study: The worldwide population shift towards older ages will inevitably lead to more elderly patients being diagnosed with non-small cell lung cancer (NSCLC). It still remains controversial whether sublobar resection is effective in such cases at an early stage. To answer this question, we need to understand the clinical characteristics of these tumors.

Material and methods: From 2004 to 2010, a total of 167 patients with stage I non-small cell lung cancer (NSCLC) of age ≥ 70 years underwent complete resection in our institution. The clinical data were retrospectively analyzed as regards gender, stage of disease, histology, smoking status, smoking amount, drinking status, surgical approaches and overall survival. Survival was analyzed by the Kaplan-Meier method and log-rank test.

Results: The overall 5-year survival rate was 62.4%. There were 122 (73.1%) patients who underwent standard lobectomy resection and 45 (26.9%) patients underwent sublobar resection. Patients with different surgical approaches (lobectomy and sublobar resection) had nearly the same 5-year survival rate (60.9% vs. 63.4%, $p = 0.558$). Gender ($p = 0.023$), smoking status ($p = 0.045$) and smoking amount ($p = 0.007$) significantly influenced the prognosis.

Conclusions: In elderly stage I NSCLC patients, sublobar resection is considered to be an appropriate treatment in comparison with lobectomy, as this procedure provides equivalent long-term survival.

Key words: elderly, non-small cell lung cancer (NSCLC), surgical resection, sublobar resection.

Early lung cancer in the elderly: sublobar resection provides equivalent long-term survival in comparison with lobectomy

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Introduction

Lung cancer is the most common cancer and the leading cause of cancer deaths in the world [1]. Surgery is considered the treatment of choice in patients with early-stage NSCLC [2]. Over the past decade, lobectomy has been the standard surgical procedure. Sublobar resection such as wedge resection and segmentectomy could be indicated in patients with stage I NSCLC, who may tolerate operative intervention but not a lobectomy resection because of comorbid disease or decreased cardiopulmonary function [3]. In recent years, retrospective studies have shown that the long-term outcome of sublobar resection is comparable to that of lobectomy [4]. Therefore, the management and determination of the appropriate operative approach for elderly patients with stage I NSCLC need an understanding of the characteristics of these tumors.

Material and methods

Patients

From 2004 to 2010, a total of 167 patients with stage I NSCLC of age ≥ 70 years underwent a thoracotomy in the Department of Thoracic Surgery, First Hospital, China Medical University. Preoperatively, patients underwent a thorough physical examination and blood examination, respiratory function test, electrocardiogram, bone scintigraphy, bronchoscopic examination and computed tomography of the brain and chest. Their clinical data were retrospectively reviewed. Variables used for evaluation were gender, stage, histology, smoking status, smoking amount, drinking status, surgical approaches and overall survival.
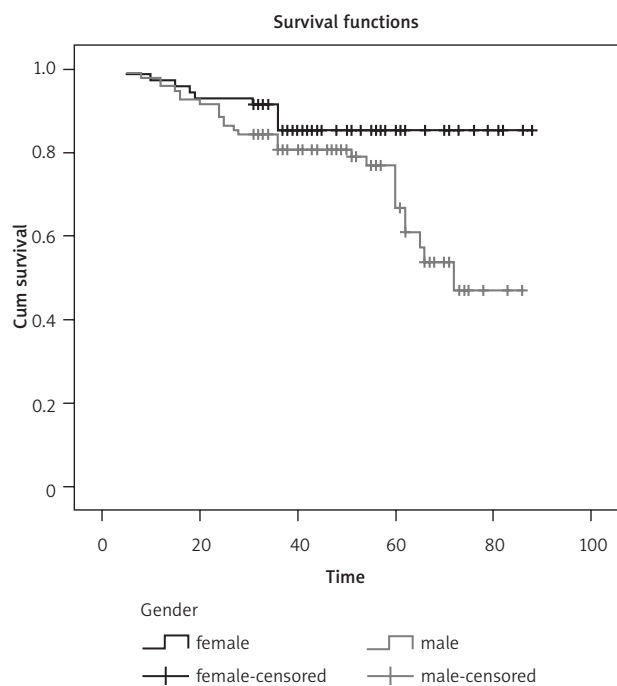
Methods

After resection, the tumors were pathologically examined during the operation with frozen section. Patients were pathologically staged according to the International Union Against Cancer (UICC) staging system for lung cancer (7th ed.) [5]. Histological subtypes of resected specimens were determined according to the World Health Organization classification of 2009. The type of surgery was categorized into two groups according to the extent of the pulmonary resection: standard surgery including a lobar resection and sublobar resection such as segmentectomy and wedge resection. A sublobar resection was indicated for high risk cases, including insufficient pulmonary function ($FEV_1 < 1.5$) or chronic lung diseases, insufficient cardiac function (LVEF < 50%) or cardiovascular diseases, or previous lung surgery (greater than lobectomy).

Table 1. Clinical characteristics of 167 patients aged ≥ 70

Variable	No. of patients	5-year survival rate	*P*-value
Total	167	62.4%	
Gender			
female	71 (42.5%)	84.2%	
male	96 (57.5%)	49.5%	0.023
Median age (range; years)	69 (65–84)		
Histology			
adenocarcinoma	98 (58.7%)	63.8%	
squamous carcinoma	62 (37.1%)	61.4%	0.749
others	7 (4.2%)	57.5%	
Surgical procedure			
lobectomy	122 (73.1%)	60.9%	
sublobar resection	45 (26.9%)	63.4%	0.558
Pathological stage			
IA	51 (30.5%)	70.6%	
IB	116 (69.5%)	58.7%	0.370
Smoking status			
smokers	77 (46.1%)	55.0%	
nonsmokers	90 (53.9%)	68.3%	0.045
Drinking status			
drinkers	32 (19.2%)	58.1%	
nondrinkers	135 (80.8%)	63.3%	0.302
Smoking amount			
PY[1] ≤ 20	48 (28.7%)	72.2%	
PY > 20	119 (71.3%)	39.5%	0.007

PY[1]: Pack-years (PY) were defined as the number of cigarette packs (20 cigarettes per pack) smoked per day multiplied by years of smoking and used to quantify smoking history.

Smoking amount was pack-years smoked (PY). Pack-years smoked was defined as the number of cigarette packs (20 cigarettes per pack) smoked per day multiplied by years of smoking and used to quantify smoking history.

Fig. 1. Kaplan-Meier survival analysis based on gender

Statistical analyses

Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. A Cox proportional hazard model was used to identify relevant variables affecting survival. Median values were shown with the 95% confidence interval (CI). Statistical analysis was performed with SPSS 16.0 software (SPSS Inc, Chicago, IL). Significance was set at *P* of less than 0.05. The overall survival time was calculated from the day of the surgery to the latest follow-up date.

Results

The clinical findings are shown in Table 1. There was no mortality or morbidity in both groups within the first 30 days. The overall 5-year survival rate was 62.4%, whereas that for females was 84.2% and that for males was 49.5% (*p* = 0.023) (Fig. 1). Of the 167 patients, 90 patients (53.9%) had no history of smoking at any time in their life as compared to 77 (46.1%) patients who had smoked. Concerning the smoking status, the 5-year survival rate for nonsmokers was 68.3%, which was better than that for smokers (55.0%); there was a statistical difference (*p* = 0.045) (Fig. 2). The overall 5-year survival rates of these patients with 20 or less PY smoking history and greater than 20 PY smoking history were 72.2% and 39.5% (*p* = 0.007; Fig. 3). The 5-year survival rate for drinkers was 58.1%, whereas it was 63.3% for nondrinkers (*p* = 0.302). The multivariate Cox proportional hazards analysis revealed that gender was associated with the hazard ratio of 0.380 (0.180–0.805; *p* = 0.012) (Table 2).
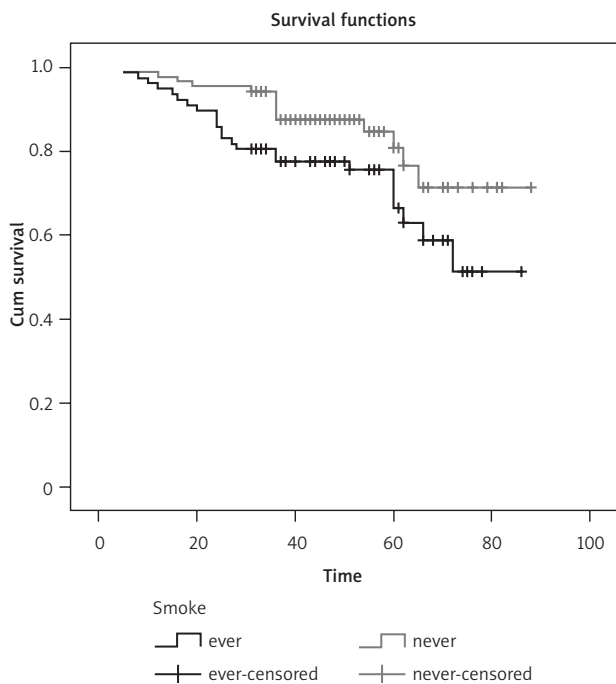
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Fig. 2. Kaplan-Meier survival analysis based on smoking status

Pack-years (PY) were defined as the number of cigarette packs (20 cigarettes per pack) smoked per day multiplied by years of smoking and used to quantify smoking history.

Fig. 3. Kaplan-Meier survival analysis based on pack-years (PY)

There was no significant difference of the 5-year survival rate in different histology, age and surgical approaches. In this study, a total of 122 (73.1%) patients underwent lobectomy resection, and 45 (26.9%) cases underwent sublobar resection. Patients receiving lobectomy had nearly the same survival rate as patients receiving sublobar resection (60.9% vs. 63.4%, p = 0.558). Fifty-one (30.5%) patients at stage IA had a 5-year survival rate of 70.6%, and 116 (69.5%) patients at stage IB had a 5-year survival rate of 58.7% (p = 0.370). The tumor histology was as follows: adenocarcinoma in 98 (58.7%) patients; squamous cell carcinoma in 62 (37.1%); others in 7 (4.2%). The 5-year survival rate for patients with adenocarcinoma was 63.8%, whereas it was 61.4% for those with squamous cell carcinoma (p = 0.749).

Discussion

Lung cancer has been the most commonly diagnosed cancer annually since 1985 [6]. With the increasing age of the global population, the number of elderly patients with NSCLC has increased. However, the surgical treatment of NSCLC in elderly patients remains challenging. In a prospective study conducted in 1995, Ginsberg *et al.* found that patients with early stage (T1N0) non-small cell lung cancer (NSCLC) who underwent limited resection had a higher locoregional recurrence and higher mortality rates than those who underwent lobectomy, and they concluded that lobectomy should be the standard surgery for stage I NSCLC [7]. Over the past decade, lobectomy combined with lymph node dissection has been the standard surgical procedure for stage I NSCLC. As aging results in physiological changes in the cardiovascular and respiratory systems, the frequency of other underlying diseases increases. Surgical resection for NSCLC itself has a possibil-
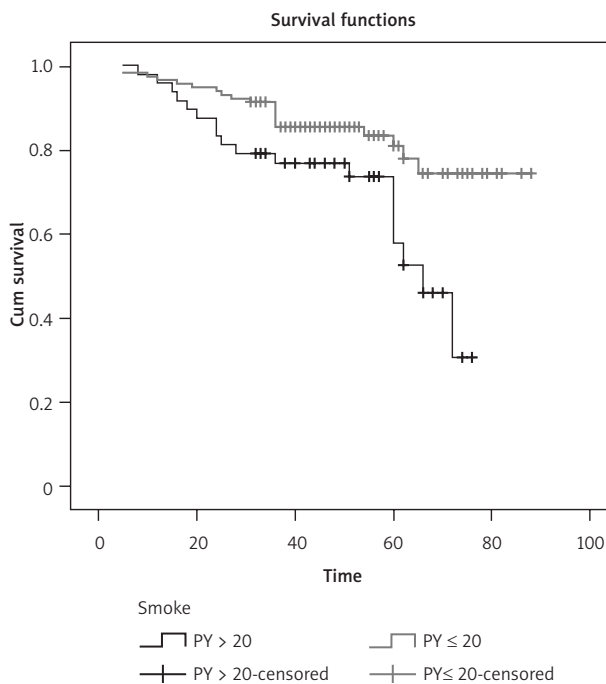
Table 2. Results of the multivariate analysis of patient characteristics (Cox proportional hazards model)

Variables	Hazard ratio	95% CI P-value	P-value
Age ≥ 70	1.044	0.520–2.098	0.903
Gender female	0.380	0.180–0.805	0.012
Smoking status never-smokers	0.761	0.259–2.234	0.619
Smoking amount[1] PY > 20	1.432	0.890–2.305	0.139
Alcohol status never-drink	0.957	0.419–2.183	0.916
Surgical procedure sublobar resection	0.737	0.350–1.552	0.422
Stage stage IA	0.678	0.321–1.432	0.309

Smoking amount[1]: Pack-years (PY) were defined as the number of cigarette packs (20 cigarettes per pack) smoked per day multiplied by years of smoking and used to quantify smoking history.

ity of increasing the risk of life-threatening complications, and the mortality rate reported ranges from 2.8% to 3.7% [8]. Thus surgeons often hesitate to recommend lobectomy for patients under comorbid conditions or with poor pulmonary function. Instead, sublobar resection such as wedge resection and segmentectomy is often offered to those patients in daily clinical practice to reduce surgical stress and to preserve more pulmonary function. In recent years, retrospective studies have shown that the long-

term outcome of sublobar resection is comparable to that of lobectomy. In 2010, Okami and his colleagues conducted a retrospective study and did not find any significant differences in 5-year survival rates between lobectomy and sublobar resection in lung cancer patients aged more than 75 years. The authors concluded that sublobar resection is the indicated surgical procedure for these patients [4]. In our study, there was a better result in the survival for sublobar resection than lobectomy. Patients who received sublobar resection had less trauma and less immune function damage, and thus they recovered quickly. This finding suggests that local control for primary early NSCLC should be considered in patients with high surgical risk or poor cardio-pulmonary functional reserve, especially for the elderly.

Cigarette smoking is a well-known risk factor in lung cancer [9]. Whether smoking-related lung cancer behaves more aggressively or results in poorer survival than lung cancer not related to smoking remains unclear. There may be several possible explanations for the highly aggressive and invasive biologic pulmonary characteristics in patients with greater than 20 PY smoking history. Cigarette smoke contains many mutagenic and carcinogenic chemicals that may be associated with mutations in tumor suppressor genes such as p53 [10]. Suzuki and colleagues [10] reported that tumors with p53 mutations exhibited an increased growth rate, which could explain why patients with greater than 20 PY smoking history resulted in poorer outcomes compared with patients with 20 or less PY smoking history. Thus a history of heavy smoking can be a simple clinical indicator for poor postoperative prognosis in patients because of its biologic aggressiveness and invasiveness.

Prognosis of lung cancer patients has been predicted reliably by disease stage [11]. However, other candidate prognostic factors in addition to stage of disease also warrant consideration [12]. One of the most important and fundamental biologic factors is gender. In our group, the survival of elderly patients with stage I NSCLC is closely related to gender. A number of studies have reported that women with NSCLC live significantly longer than men after surgical or non-surgical treatment [13–15]. Several confounding factors associated with gender may influence survival in NSCLC. One representative factor is a difference in smoking status between genders. Smoking behavior is closely associated with social custom, and female/male smoking ratios are quite different between various regions and years of publication [16, 17]. Because smoking may be the worst prognostic factor in lung cancer [18, 19], differences in smoking status prevalence could result in significant differences in survival outcome between genders.

However, some problems of our study are as follows. This study was retrospective, and surgery was performed in a selection-biased population. Reporting inaccuracies and other subtle selection biases are possible and may distort the results of the study. Secondly, sublobar resection cannot provide as much information for a final staging as lobectomy. Third, we should recognize that such retrospective analyses were inherently affected by predilections for several patients' factors between the types of surgery and the selection bias associated with surgical procedure. The lobectomy group may comprise younger patients and had a different racial mix. It is possible that healthier patients instead of sicker patients were offered lobectomy resection. These are known to be favorable prognostic factors in these patients.

In conclusion, sublobar resection in the elderly provides a long-term outcome which is equivalent to that obtained after standard lobectomy. Thus in patients who cannot tolerate a lobectomy, a lung-sparing procedure, such as wedge resection and segmentectomy, also appears to offer survival benefit. However, a large sample study with matching patients is necessary to confirm the equivalent results between the two surgical procedures.

Authors declare no conflict of interest.

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