Ann Thorac Cardiovasc Surg 2019; 25: 95–101
Online December 11, 2018
doi: 10.5761/atcs.oa.18-00206

Original Article

Is the Outcome of Pulmonary Resections due to Non-Small Cell Lung Cancer in Octogenarian Patients Worse?

Ali Cevat Kutluk, MD, Hasan Akin, MD, Altan Ceritoglu, MD, Celalettin Ibrahim Kocaturk, MD, Salih Bilen, MD, Yasar Sonmezoglu, MD, and Kemal Karapinar, MD

Purpose: Lung cancer is one of the major sources of mortality in the elderly. This study was undertaken to assess the early and long-term results of surgical resection in patients older than 70 years of age by comparing the results of patients aged 70–79 years (group 1) with patients older than 80 years of age (group 2).
Methods: Data on patient age, gender, spirometry values, side, size, histology and stage of the tumor, surgical procedures, postoperative complications, Charlson comorbidity scores (CCS), and survival were collected.
Results: After 1–2 propensity score matching group 1 (70–79 years) included 84 and group 2 (age over 80) 42 cases. The multivariate analysis showed that CCS was the only significant factor affecting the development of complications (p = 0.003). The overall median and 5-year survival of all patients were 55 months and 42.5%, respectively. Although the survival of the elderly group 2 was higher than the first group, the difference did not reach significance (50 vs. 49 months, respectively).
Conclusion: The outcomes of surgery in terms of morbidity and mortality rates do not differ between the two age groups. The safety of pulmonary resections in the elderly group is comparable to patients under 70 years if the comorbidities are appropriately controlled. In addition, surgery provides satisfactory survival rates in both age groups.

Keywords: octogenarian, non-small cell lung cancer, surgery

Introduction

According to the data of Turkish Statistical Institute, the general age of the population in Turkey is increasing as other countries in Europe.[1] Turkish public health institution department of cancer stated that non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death in people older than 70 years.[2] Advances in anesthetic management and surgical techniques have enabled surgeons to include increasing numbers of elderly patients in surgical series. Although the complete surgical resection is still the gold standard in treating the early stage lung cancer, increased rates of co-existing cardiopulmonary and cerebrovascular conditions place the elderly patients in more hazardous situation when compared to younger patients. Performing surgery in this age group could sometimes be challenging for a thoracic surgeon.

This study was undertaken to assess the early and long-term results of surgical resection in patients older than 70 years of age by comparing the results of patients aged 70–79 years with patients older than 80 years of age.

Department of Chest Surgery, Yedikule Chest Diseases and Surgery Training and Research Hospital, Istanbul, Turkey

Received: August 29, 2018; Accepted: September 25, 2018
Corresponding author: Ali Cevat Kutluk, MD. Department of Chest Surgery, Yedikule Chest Diseases and Surgery Training and Research Hospital, C. No.1, Zeytinburnu, Istanbul 34020, Turkey
Email: dralikutluk@gmail.com

Material and Methods

A retrospective analysis was performed in patients who underwent resection due to NSCLC at our center between January 2006 and December 2015. Our hospital is one of the largest lung cancer centers across the country in which about 15 full-time surgeons perform the operations with 15 surgical trainee fellows. Patients coming from all parts of the country are evaluated by a council consisting of thoracic surgeons, pulmonologists, oncologists, radiologists, and pathologists. Clinical data were obtained from the records of archive department and the surgical reports stored in information technology (IT) department.

All patients had a detailed assessment based on history, symptoms, and signs of chronic lung or heart disease. Chest X-ray, thorax computed tomography (CT), electrocardiogram (ECG), arterial blood gas analysis, pulmonary function tests, and biochemical tests were performed. Since 2005, all patients underwent positron emission tomography (PET) -CT for possible mediastinal lymph node and distant metastases. Fiber optic bronchoscopy (FOB) was performed to reveal the location of the tumor in the bronchus and to take biopsies to diagnose the tumor. For peripherally located tumors trans-thoracic needle aspiration biopsy (TTNB) was performed for diagnosis. Tumor staging was done according to the 7th staging of lung tumors.[3] All patients performed pulmonary function tests, and patients with the postoperative forced expiratory volume in one second (FEV1) value or carbon monoxide diffusing capacity (DLCO) value below 40% of predicted were directed to advanced tests, namely stair climbing or cardiopulmonary exercise test (VO_2max). Patients with limited respiratory functions were directed pulmonary rehabilitation department and rehabilitation was given for 2 weeks. Patients who smoked for the last month were not taken to surgery. Patients who lost 5% of body weight in the last 3 months were supported by the nutrition team of the hospital. Cardiology consultation was provided for all cases. Mediastinoscopy and/or endobronchial ultrasonography (EBUS) (since 2013) were performed routinely except for tumors located peripherally, seized less than 2 cm, and with squamous cell histology. The comorbidities of all patients were noted and Charlson comorbidity scores (CCS) was calculated.[4] Preoperatively, patients were informed about the operation and enforced smoking cessation.

All cases were intubated with a double lumen endotracheal tube, and either muscle sparing postero-lateral thoracotomy or video-assisted thoracoscopic surgery was undertaken. Systematic mediastinal lymph node dissection was performed in all cases. Prophylactic antibiotic (second generation cephalosporins) was administered both at the induction of anesthesia and 3 h after surgery. Extubation was performed in all cases in the operation theatre. Patients were followed in the intensive care unit at the day of the operation, and pain management was achieved by patient controlled analgesia. Follow-up policy was to see the patients every 3 months for the first 2 years, every 6 months between 2 and 5 years, yearly then on with chest tomography.

Major complications were defined as pneumonia, respiratory failure, bronchopleural fistula, empyema, myocardial infarction, lobar atelectasis, acute renal failure, major bleeding, and wound infection requiring intervention. Minor complications were defined as air leakage for more than 7 days, new-onset of atrial fibrillation/flutter, sinus tachycardia, superficial wound infection, and segmental atelectasis requiring no intervention. All complications were classified into four grades of postoperative complications as per Clavien-Dindo classification criteria.[5] Operative mortality was defined as all deaths occurring within 90 days of surgery either at the hospital or outside the hospital.

Data on patient age, gender, comorbidities, spirometry values, blood gas analysis results, surgical side, size of the tumor, surgical procedures (lobectomy vs. sublobar resection vs. pneumonectomy), and histology of the tumor, pathological classification of malignant tumors (TNM) stage, postoperative complications, and survival were collected. Patients who had an exploratory thoracotomy, with neoadjuvant therapy, with incomplete resection, and patients with insufficient data were excluded from the study (**Fig. 1**).

The retrospective review of medical records and radiographic findings was approved by the Institutional Review Board of Istanbul Research and Training Hospital (1136/12.01.2018).

Statistical analysis

The data of the two groups were compared by univariate analysis. For categorical variables Pearson's chi-squared test and for continuous variables Student's t-test was used. Propensity score matching method was used to minimize the influence of other confounders. Group 2 patients were matched in a 1 to 2 ratio with group 1 using the nearest neighbor matching (**Table 1**). To identify the factors associated with morbidity and mortality, multivariable logistic regression was used. Kaplan–Meier survival analysis was used to calculate the overall survival,

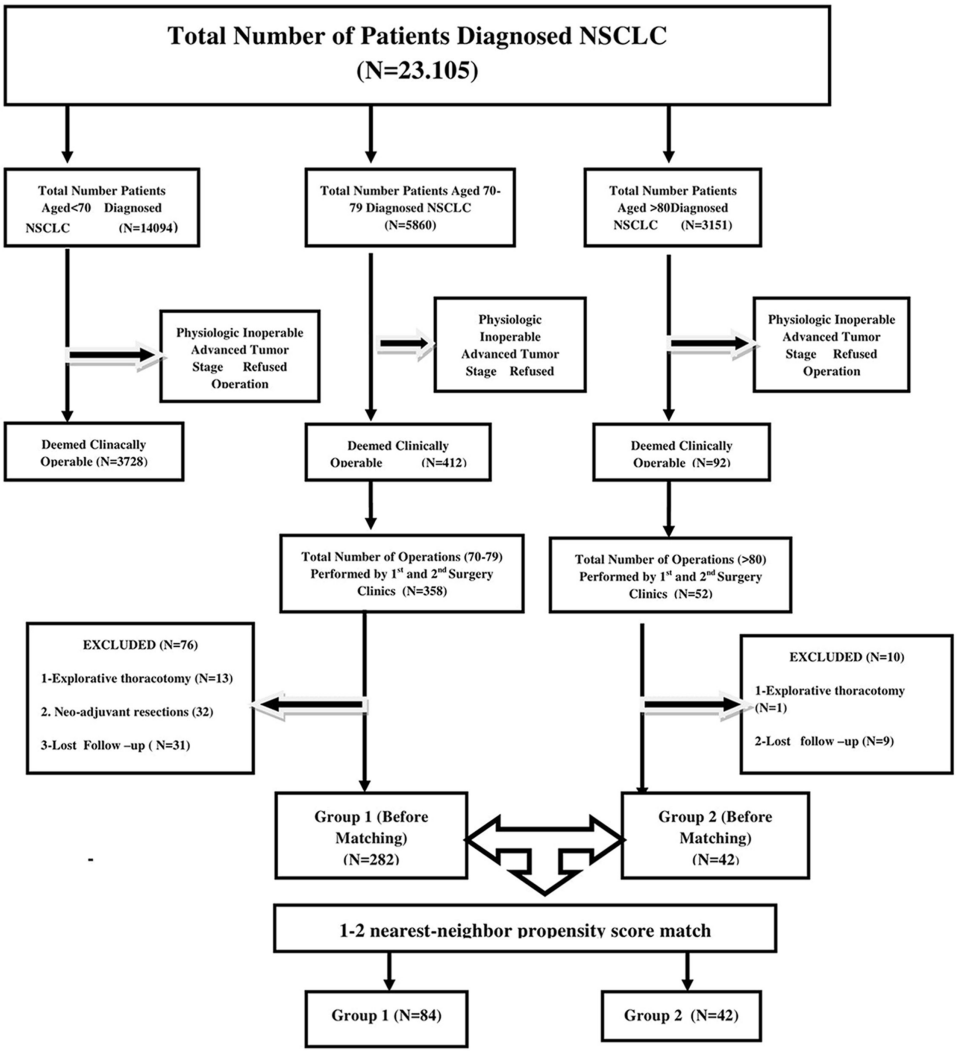

Fig. 1 Flow chart showing the path of the patients in the study. NSCLC: non-small cell lung cancer

and the log-rank test was used to compare survival between groups. A p value of less than 0.05 was considered statistically significant.

IBM SPSS Statistics, version 23 for Windows (IBM Corporation, Armonk, NY, USA) was used to execute the calculations. Since the SPSS ver. 23 did not include the function of propensity score analysis, we used software R (The R Foundation for Statistical Computing, Vienna, Austria) and installed the extension of propensity score matching package.[6)]

Results

During this period, 4232 patients underwent surgery, 324 (7.6%) of them who were 70 years or older constituted the study group. Patients were divided into two groups based on the age: group A aged between 70 and 79, group B age 80 and over (**Fig. 1**). The rates of surgery in the younger and the older group were 7.5% and 3%, respectively. This rate was 26% in all patients who were below the age of 70 years.

Clinical characteristics of the two groups before and after matching are depicted in **Table 2.** Non-squamous histological type and the FEV1 levels were significantly higher in the elderly group. For each variable, the absolute mean differences were found to be less than 0.1 after matching which indicated the balance between the groups.

The overall morbidity rate was calculated as 44.7% (145 patients out of 324) and was similar in both groups (45.1% vs. 43.4%). Arrhythmia was the most common complication in the elderly group, whereas prolonged air leak was the leading complication in group 1 (**Table 1**).

Table 1 The distribution and comparison of the postoperative complications of the two groups graded according to Clavien-Dindo

Grade	Complications	Group 1 n (%)	Group 2 n (%)	P
I	Wound infection	13 (4)	2 (4.4)	0.37
II	Arrhythmia	47 (13)	11 (24)	***0.04***
II	Pneumonia	33 (9.5)	4 (8.5)	0.57
II	Acute renal failure	11 (3)	2 (4)	0.42
IIIa	Prolonged air leak	49 (14)	8 (17)	0.32
IIIa	BPF + empyema	7 (2.5)	1 (2.2)	0.66
IIIa	Respiratory failure	21 (6)	4 (8.5)	0.31
IIIB	Postoperative bleeding	14 (4)	1 (2)	0.47
IVa	Myocardial infarction	4 (1)	0 (0)	0.63

BPF: bronchopleural fistula

The factors affecting the morbidity are shown in **Table 3**. Patients with comorbidities developed one or more complications than patients without comorbidities, and the difference was found significant (p = 0.003).

Twenty-one out of 324 (6.4%) patients died at the 3-month mortality period, the mortality rates were similar in both groups (6.3% vs. 7.1%). In contrast to the morbidity, patients with comorbidities did not have higher mortality rate than the patients without comorbidities, p = 0.237 (**Table 3**).

The overall median and 5-year survival of all patients were 55 months and 42.5%, respectively (**Fig. 2**). In univariate analysis, only the N factor (N2 disease) affected the survival significantly (50.13 months vs. 33.46 months). There was no significant difference of survival between groups 1 and 2 (49.03 months vs. 50.90, respectively, p = 0.82). In multivariate analysis with Cox regression through the presence of N2 disease has a p value of 0.07, no factors were found affecting the survival (**Table 3**).

Discussion

In the elderly population, lung cancer remains an important source of mortality when not treated appropriately. In operable patients, pulmonary resection occupies the center of the treatment. It is not surprising that older patients have less life expectancy and so less postoperative survival when compared to younger patients. The chronological age does not always reflect the patients true physical and mental conditions. However, it is crucial to select the appropriate patient and decide the suitable surgical approach in this age group.

In the present study, nearly half of the patients suffered from complications. Arrhythmia and the prolonged air leak were found the leading complications in both cases; nevertheless, arrhythmia were significantly higher in the elderly group (24% vs. 13%). Except for the high comorbidity index, no other factors such as FEV1, type of resection, or size of the tumor affected the complication rate in multivariate analysis. Baldvinsson et al. reported that complication rates were 13% and 11% in patients aged younger than 75 and older 75, respectively.[7] Similar to the current series, cardiac complications and prolonged air leak are the leading complications. Berry et al. reported a higher complication rate of 46% in 193 octogenarian patients with arrhythmias and prolonged air leak as the leading complications. In that series, morbidity rate is affected negatively by resection greater than wedge, thoracotomy as operative approach, and % predicted forced expiratory volume in 1 second.[8] Gore et al. stated in a review that comorbidity in lung cancer patients increases with age, and comorbidities cause decreased performance status and increased weight loss. However, he also stressed that performance status, comorbidities, and age at diagnosis are independent prognostic factors.[9]

Unlike the case in morbidity rates that were affected negatively by the high Charlson comorbidity index (CCI), there was no significant factor affected the mortality. The 30-day-mortality rate is 4.6% (15 patients) in the current study and similar in both groups. In the literature, the mortality rate is between 2.2% and 9% in patients aged between 70 and 79 years.[10–12] The lower mortality rate in Cerfolios series could be relatively lower number of patients with pneumonectomy (4%).[10] Detillion et al. reported 2.6% mortality rate in 934 patients but the study excluded the patients with pneumonectomy (176 patients).[11] The high rates of pneumonectomy and bilobectomy (30%) in the Norwegian study accounted for the 9% mortality rate of the study.[12] In the current study, the rate of pneumonectomy is nearly 16% and the

Table 2 Clinical characteristics of the two groups before and after matching

GROUPS	BEFORE MATCHING			AFTER MATCHING		
	Group 1 n (%)	Group 2 n (%)	p	Group 1 n (%)	Group 2 n (%)	p
Sex			0.18			***0.04***
Male	234 (83)	32 (76)		75 (89)	32 (76)	
Female	48 (17)	10 (24)		9 (11)	10 (24)	
Tumor Side			0.07			0.26
Right	149 (53)	26 (62)		46 (55)	26 (62)	
Left	133 (47)	16 (38)		38 (45)	16 (38)	
Type of Resection			0.11			0.43
Lobectomy	197 (70)	29 (69)		65 (77)	29 (69)	
Pneumonectomy	44 (15.8)	3 (7)		14 (17)	3 (7)	
Sublobar	18 (6.2)	6 (15)		2 (2.5)	6 (15)	
VATS Lobectomy	23 (8)	4 (10)		3 (3.5)	4 (10)	
Size of Tumor	4.4±2.12	4.3±2.37	0.77	4.2±2.36	4.3±2.37	0.74
Tumor Histology			***0.001***			0.35
Squamous	130 (48)	18 (43)		44 (52)	18 (43)	
Non-Squamous	141 (52)	24 (57)		40 (48)	24 (57)	
T Status			0.68			0.8
T1	56 (20)	11 (26)		20 (24)	11 (26)	
T2	124 (44)	21 (49)		39 (46)	21 (49)	
T3	76 (27)	8 (21)		18 (21)	8 (21)	
T4	26 (9)	2 (4)		7 (9)	2 (4)	
N Status			0.85			0.9
N0	177 (63)	28 (66)		60 (71)	28 (66)	
N1	90 (32)	12 (30)		21 (25)	12 (30)	
N2	15 (5)	2 (4)		3 (4)	2 (4)	
FEV1	1.94±0.78	1.72±0.46	***0.01***	1.83±0.43	1.72±0.46	***0.04***
FEV1 %	75.54±18.67	89.57±23.47	***0.008***	78.62±19.04	89.57±23.47	0.07
PaO2 (mmHg)	80.66±11.05	78.25±13.38	0.19	71.21±14.42	78.25±13.38	0.53
Comorbidites	**187 (69)**	**32 (72)**	**0.73**	**60 (71)**	**32 (72)**	**0.89**
Cardiac	143 (53)	25 (55)		43 (51)	25 (55)	
Respiratory	89 (34)	13 (29)		26 (31)	13 (29)	
Renal	14 (5)	3 (6)		4 (5)	3 (6)	
Neurologic	11 (4)	1 (2)		2 (2.3)	1 (2)	
Metabolic (DM)	54 (20)	10 (23)		18 (21)	10 (23)	

FEV1: forced expiratory volume in one second; VATS: video-assisted thoracoscopic surgery

mortality rate is 4.6%. In contrast, the mortality rates of octogenarian patients range between 0% and 21% in the literature.[13] The extreme rates of mortality in the series could be due to relatively lower number of patients (mean: 35 patients). However, the series with the large volume of patients (over 350 patients) reflected a mortality rate of around 6%.[14]

In different series, the type surgery (lobectomy vs. pneumonectomy), performance status, age, sex, low body mass index, and pulmonary reserve are reported to be important factors for mortality rates. In a large series with 1102 patients, age, male sex, poor pulmonary status, performance status, and the presence of comorbidities (cardiac) are reported affecting the mortality significantly.[11]

Table 3 Cox-regression analysis of the factors affecting morbidity, mortality, and the survival

Factors	Morbidity		Mortality		Survival	
	p	Exp (B)	p	Exp (B)	p	Exp (B)
Propensity score	0.724	0.408	0.144	0.812	0.545	0.451
CCI	***0.003***	***3.034***	0.237	0.373	0.149	1.334
FEV1	0.618	0.803	0.855	0.946	0.825	1.051
Sex	0.090	0.168	0.439	0.688	0.723	1.099
Type of resection	0.265	1.260	0.237	0.531	0.768	0.954
Group	0.659	0.762	0.771	0.644	0.783	0.927
T status	***0.077***	***2.055***	0.494	0.688	0.737	0.934
N2 disease	0.904	1.116	0.959	1.065	***0.07***	***2.325***
Histopathology	0.980	1.014	0.236	2.293	0.444	1.184

CCI: Charlson comorbidity index; FEV1: forced expiratory volume in one second

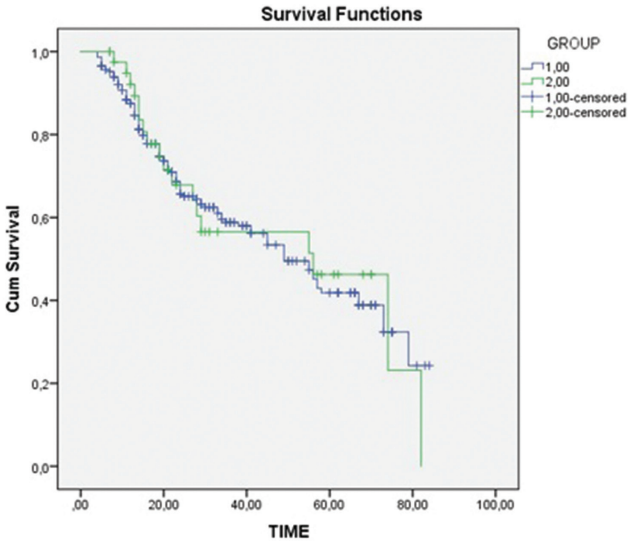

Fig. 2 The survival analysis of the two groups.

Shiono et al. reported that increased surgery time and surgery before 2004 affected the mortality rates negatively.[15] In a small series, Naunheim et al. reported that only age affected the mortality other than the type of surgery or presence of comorbidity.[16]

The overall 5-year survival of the current series is 42.5% and the survival of the two groups is very similar, so much that the elderly grouped survived a little longer. In the literature, the survival rates ranged from 24% to 66%.[13] Okami et al. reported one of the highest survival rates in 367 patients with a 56% survival rate.[17] In series published before 2005, the 5-year survival rates are around 30%.[18,19] The extent of the resection, preoperative pulmonary functions, performance status, gender, comorbidities, body mass index, and stage of the tumor have been reported as prognostic factors for the survival.[20,21]

Okada et al. reported in a series with 40 cases that the 5-year survival of patients with limited resections (segmentectomy and wedge resection) is comparable to radical lobectomy and he also suggested that limited resections had lower morbidity and mortality rates.[22] In contrast, Dominguez-Ventura et al. reported that sublobar resections have poorer survival when compared to lobar resections.[14] This difference may be due to patient selection bias because sublobar resections are generally performed in patients with limited pulmonary functions or high comorbidity scores. In the current series, the rate of limited resections was found 6 times (15% vs. 2.5%) more common in the elderly group, whereas the rate of pneumonectomy was lower in this age group (7% vs. 17%). But the type of resection was not found as a factor affecting the 5-year survival rate.

The main limitations of the study are that this is a retrospective study and the relatively small sample size of the group 2 patients (age over 80). To minimize the selection bias, we used propensity score matching.[23] Our hospital is a not a general hospital which is specialized in chest diseases and thoracic surgery. There is no geriatrics department. Also the number of video-assisted thoracoscopic surgery (VATS) resection is low because VATS has been used since the last 5 years in a progressive fashion.

Conclusion

Although lung resection in octogenarians has relatively higher morbidity and mortality rates, these risks have decreased to acceptable rates. The study showed that with better patient evaluation and better control of comorbidities, surgery is safe in octogenarian patients with acceptable

morbidity and mortality rates. In 1990s, the safety of the surgery in septuagenarians was the issue discussed among thoracic surgeons, but maybe in near future studies researching the safety of pulmonary resection in the 9th and even in the 10th decade will be published.

Disclosure Statement

The authors declare no conflict of interests and financial support.

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