

ORIGINAL ARTICLE

Clinical patterns and treatment outcome in resected elderly lung cancer patients

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Summary

Purpose: Lung cancer is the leading cause of cancer related morbidity and mortality worldwide. The aim of this study was to determine the clinical patterns and their impact on surgical resection in patients with non-small cell lung cancer (NSCLC) > 70 years.

Methods: We reviewed the records of 2050 resected lung cancer patients in a 5-year period from 2002-2007, out of whom 93 were > 70 years.

Results: There were 73 males and 20 females with median age of 71 years (range 70-78). Nineteen (20.43%) patients underwent pneumonectomy, 6 (6.45%) extended pneumonectomy, 54 (58.06%) lobectomy, 8 (8.61%) extended lobectomy, and 3 (3.23%) bilobectomy and wedge resection each. There were 37 (39.8%) resected patients with locally

advanced (IIIA, IIIB) or advanced stage (IV) of NSCLC. A total of 48 complications occurred. The 30-day mortality rate was 1.08% (one patient). Pathological stage ($p < 0.001$) and application of adjuvant therapy ($p < 0.001$) were predictors of long-term survival. The overall 3- and 5-year actuarial survival rates were 46% and 28%, respectively.

Conclusion: Advanced age should not be considered as a contraindication for NSCLC resection. However, careful preoperative assessment must be undertaken. The presence of comorbidities and extent of resection predict increased operative risk. Pathological stage and application of adjuvant therapy were the only predictors of long-term survival.

Key words: lung cancer, older age, surgical resection, survival, treatment

Introduction

Lung cancer is the leading cause of cancer mortality, and it is estimated that more patients die of lung cancer than of breast and colon cancer [1]. The World Health Organization (WHO) estimates that the number of people older than 65 years with cancer is expected to double during the first 25 years of the new millennium [2]. In 2000, 1.3 million people had cancer, and in 2025 will be 800 million people > 65 years, with 2.6 million cancer patients [3]. The median age at diagnosis of lung cancer in Western countries is 69 years [4]. Approximately 85% of the patients have NSCLC, and at the time of diagnosis the majority of patients have locally advanced or metastatic disease. Only 35% of the

patients with NSCLC present with early-stage disease, defined as stage I and II disease, and a selected group of patients with stage IIIA with surgically resectable disease [5]. Surgical resection remains the treatment of choice for early-stage NSCLC, but the surgical risk becomes higher with age because of increased prevalence of comorbidities and poor performance status [6].

The aim of this study was to analyse the clinical findings, the comorbidities and the long-term survival in a cohort of 93 septuagenarians operated for NSCLC.

Methods

We reviewed the medical records of patients who

had undergone lung resection for NSCLC between January 2002 and December 2007. Almost all patients (91; 97.85%) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1. Assessment included history, physical examination, routine blood tests, electrocardiogram, blood gas analysis, spirometry, and in selected cases echocardiography and CO diffusion capacity of the lung. Clinical staging was based on bronchoscopy, CT of the chest, abdomen and brain, as well as bone scintigraphy. Coronary artery disease was defined as a history of myocardial infarction, coronary stenting or bypass and angina pectoris. One patient had a previous malignancy (basal cell skin cancer), diagnosed < 5 years, with no evidence of active disease at the time of evaluation for new primary lung cancer. Histologic typing was assessed according to WHO criteria, while clinical and pathologic stages were determined according to the international TNM classification for lung cancer [7,8]. Postoperative complications were classified as minor (non-life-threatening) or major (potentially life-threatening). Operative mortality was defined as death within 30 days from surgery or during the same hospitalization. The standard follow-up protocol included a total-body CT scan, blood and laboratory tests (serum albumin, lactate dehydrogenase and alkaline phosphatase levels), spirometry and blood gas analysis every 6 months for the first 2 years, then every 12 months until the 5th year. Bronchoscopy was performed only in cases of suspected recurrent disease. Adjuvant therapy was administered when lymph node disease or residual disease was found on pathologic examination of specimens. Follow-up information was obtained either during office visits or by telephone with patients, relatives or physicians. Survival was defined as the interval between the date of surgery and date of death or last follow up. Deaths included all cases, but we separated cancer and non-cancer related deaths.

Statistical analysis

The statistical package used was R (version 2.8.0 (2008-10-20); Copyright (C) 2008 the R Foundation for Statistical Computing; ISBN 3-900051-07-0. Data are reported as mean \pm standard deviation (SD). Survival rate was estimated by the Kaplan-Meier method. Other comparisons were made using Mann-Whitney U test, Pearson's χ^2 test, Fisher's exact test, Wilcoxon signed rank test. Significance was accepted as a p-value of < 0.05.

Results

From 2002 to 2007, there were 93 septuagenarians, representing 4.53% of 2050 lung resections per-

formed during that period. There were 73 males and 20 females, aged 70-78 years (median 71). The basic characteristics are summarized in Table 1. Most had a history of cigarette smoking (n=55; 59.14%) with 40 median pack/years, 31.18% were ex-smokers, and 9.68% were non-smokers. The median value of forced expiratory volume in 1 second (FEV₁) was 106% of the predicted value (range 66.2-152). Comorbidities were noticed in 85 (91.40%) patients and chronic obstructive pulmonary disease (COPD) was the most prevalent in 40 (43.01%) patients, followed by arterial hypertension in 19.35%, coronary artery disease and arrhythmias in 10.75% patients each (Table 2). In COPD patients, FEV₁ (%) was 79.12 \pm 18.92. We noticed that there was significant difference in preoperative values of FEV₁ according to smoking habits (p=0.00028), especially in relation of ex-smokers to non-smokers (p=0.00031), and non-smokers to smokers (p=0.0027). Postoperative values

Table 1. Demographic, clinical and pathological characteristics of 93 septuagenarians

Characteristics	No. of patients (%)
Mean age \pm SD (years)	71.73 \pm 2.04
Sex (male/female)	73/20
Smoking habits	
Current smokers	55 (59.14)
Ex-smokers	29 (31.18)
Non-smokers	9 (9.68)
Comorbidities	85 (91.40)
>1 comorbidity	49 (52.69)
Respiratory parameters (mean \pm SD)	
FEV ₁	93.17 \pm 20.32
FVC	106.2 \pm 17.26
PaO ₂ mmHg	76.32 \pm 9.79
Pathological stage	
I	15 (16.13)
II	41 (44.08)
III	33 (35.48)
IV	4 (4.30)
Histology	
Squamous cell carcinoma	61 (66.67)
Adenocarcinoma	29 (46.03)
Large cell carcinoma	3 (3.23)
Induction therapy	5 (5.37)

Table 2. Comorbidities of 93 septuagenarians undergoing lung resection

Comorbidity	No. of patients (%)
Chronic obstructive pulmonary disease	40 (43.01)
Arterial hypertension	18 (19.35)
Coronary artery disease	10 (10.75)
Arrhythmias	10 (10.75)
Diabetes mellitus	4 (4.3)
Peripheral neurologic disease	2 (2.15)
Previous malignancy < 5 years	1 (1.07)

of FEV₁ in COPD patients were significantly lower 3 and 6 months after the operation ($p < 0.001$), as well as one year postoperatively (70.3 ± 17.29). More than half of the patients ($n = 54$; 58.06%) had undergone lobectomy, 19 (20.43%) pneumonectomy, 8 (8.61%) extended lobectomy, 6 (6.45%) extended pneumonectomy and 3 (3.23%) patients bilobectomy and wedge resection each (Table 3). There were 31 cases defined as stage IIIA, out of whom 20 as N2 disease, T3N1 disease in 8 cases, and T4N1 in 3 cases. In stage IIIB there were 2 cases, and 4 in stage IV disease (Table 4). A total of 48 perioperative complications occurred (Table 5). Arrhythmia was the most common disorder. Seventeen (18.28%) patients

developed arrhythmia postoperatively, renal failure and hematemesis in one each (1.08%) patient each. Respiratory complications included 8 (8.6%) patients who developed pneumonia, 6 (6.46%) atelectasis, 4 (4.30%) empyema, 2 (2.16%) respiratory failure and one (1.08%) bronchopleural fistula. There were no patients who required mechanical ventilation postoperatively.

Five patients received neoadjuvant therapy; chemotherapy 4 (4.3%) and radiotherapy one (1.08%) case. Adjuvant chemotherapy was administered to 6 cases, concomitant chemotherapy and radiotherapy in 26 and radiotherapy alone in 7 cases (Table 6). Cancer was the most prevalent cause of death in 78/93 patients. Among

Table 3. Type of resection according to pathological (p) stage

Type of resection	p stage						
	I		II		III		IV
	IA	IB	IIA	IIB	IIIA	IIIB	
Pneumonectomy		1	5	5	7	1	
Extended pneumonectomy				1	4	1	
Lobectomy	4	7	15	10	16		2
Extended lobectomy		2	3		2		1
Bilobectomy			1	1			1
Wedge resection		1			2		

Table 4. Characteristics of 6 resected patients with locally advanced and advanced NSCLC

Age (years)	Gender	Comorbidity	Surgical procedure	Pathological stage	Histological type	Overall survival (months)
70	Female	Hypertension	Pneumonectomy	T4N2M0	Adenocarcinoma	18
72	Male	Hypertension	Extended pneumonectomy	T4N2M0	Adenocarcinoma	15
73	Male	None	Extended lobectomy	T2N0M1b	Adenocarcinoma	14
72	Male	COPD	Extended lobectomy	T2N0M1b	Squamous cell carcinoma	30
73	Male	Hypertension	Bilobectomy	T2N1M1b	Adenocarcinoma	4
74	Male	COPD	Lobectomy	T2N1M1b	Adenocarcinoma	35

COPD: chronic obstructive pulmonary disease

Table 5. Postoperative complications in 93 septuagenarians undergoing lung resections

Complications	No. of patients (%)
Major complications	
Atrial fibrillation	17 (18.28)
Pneumonia	8 (8.6)
Empyema	4 (4.30)
Respiratory failure	2 (2.16)
Bronchopleural fistula	1 (1.08)
Renal failure	1 (1.08)
Hematemesis	1 (1.08)
Minor complications	
Atelectasis requiring bronchoscopy	6 (6.46)
Repeat thoracotomy	8 (8.68)

Table 6. Adjuvant therapy according to stage of disease

Adjuvant therapy	Stage		
	IIIA n (%)	IIIB n (%)	IV n (%)
Chemotherapy	–	2 (100)	4 (100)
Chemo/radiotherapy	24 (77.42)	–	–
Radiotherapy	7 (22.58)	–	–

non-cancer related deaths we noticed sudden death in 5 (5.37%), heart failure in 4 (4.3%), pulmonary embolism in 2 (2.15%), pneumonia, sepsis, cerebrovascular accident and suicide in one (1.07%) patient each.

Survival

Survival according to adjuvant therapy was significantly different (log-rank test, $p < 0.001$). Median survival without therapy was 20 months (95% CI 15-32), with chemotherapy 18 months (95% CI 6-24), with concomitant chemo and radiotherapy 7 (95% CI 6-12) months, (Figure 1). On the other hand, survival according to preoperative FEV₁ (< 70 vs. >70%) was not significantly different (log-rank test, $p = 0.78$). Median survival with FEV₁ < 70% was 31.5 months (95% CI 20-39) and median survival with FEV₁ >70% was 34 months (95% CI 24-42), (Figure 2). The overall survival in 93 septuagenarians at 1, 2, 3, 4, 5 years was 80.64, 59.98, 46.05, 31.81 and 28.63%, respectively (Figure 3). At a mean follow-up of 60 months, 38 (40.86%) patients were alive and 55 (59.14%) had died. The cause of late death was cancer-related in 78/93 (83.87%) patients.

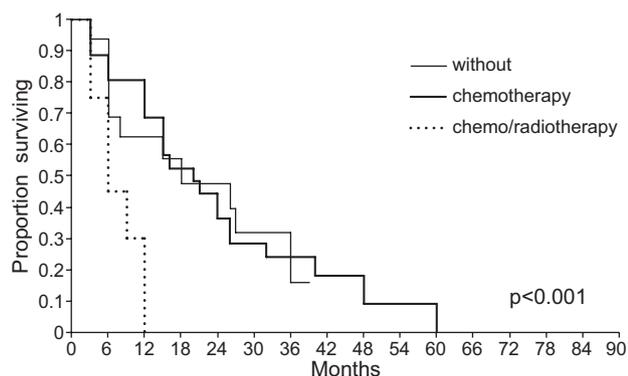


Figure 1. Overall survival according to adjuvant therapy in 93 septuagenarians.

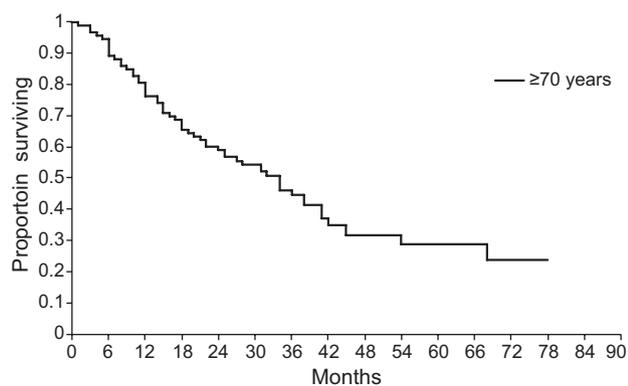


Figure 3. Overall survival in 93 septuagenarians.

The overall 3- and 5-year actuarial survival rates were 46.05 and 28.63%, respectively (Figure 3).

Survival according to pathological stage was significantly different (log-rank test, $p < 0.001$). Median survival in stage I was 48 months (95% CI 41-54), in stage II 34 months (95% CI 31-43), in stage III 18 months (95% CI 12-28) and in stage IV 4 months (95% CI 4 - not available) (Figure 4).

Discussion

The results of the present study showed that careful patient selection, preoperative evaluation of cardiopulmonary status and comorbidities before surgery are essential. The final decision for NSCLC resection should not be based only on age.

The world population is aging, and the proportion of elderly patients with lung cancer is increasing. In this study we considered patients ≥ 70 years old as elderly, but there is no clear definition for this distinction. The age of 70 years is considered to be the cut-off point [9].

The selection of the type of resection should be

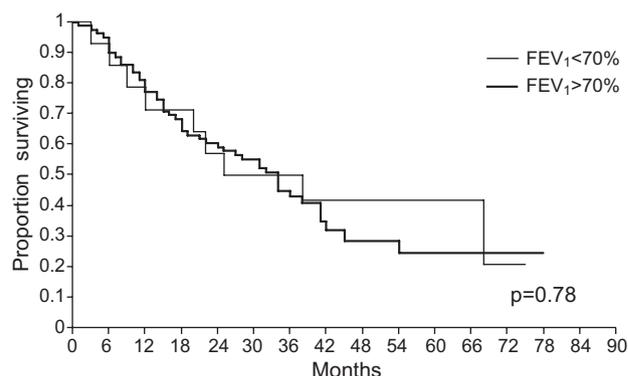


Figure 2. Overall survival according to preoperative $70\% < FEV_1 < 70\%$.

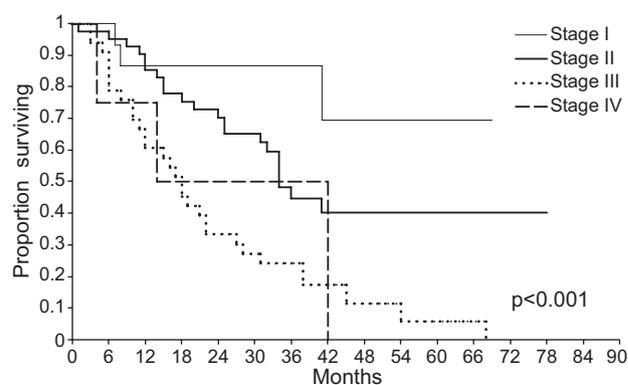


Figure 4. Overall survival according to pathological stage in 93 septuagenarians.

based on lung function values. According to our data that 84 (90.32%) patients were current or ex-smokers and the presence of COPD was the most prevalent comorbidity, we can conclude that lung function in our case series was additionally disturbed. Our results showed significantly lower postoperative values of FEV₁ in COPD patients and among smokers or ex-smokers. Ishida and al. showed that there is a connection between Brinkman index (number of cigarettes smoked per day x the number of years of smoking) and postoperative complications in patients > 70 years, with a value of 801 being the critical number which is equivalent to 40 pack/year smoking history [10]. The incidence of adenocarcinoma in patients > 70 years was significantly lower than squamous cell carcinoma as was previously reported [11].

Although several previous studies [12-14] showed that elderly patients more often present in earlier stages, possibly due to the slow progress of lung cancer in the elderly, this was not the case in our series, since more than one third of patients were in stage III. Contrary to other results, there were 37 (39.78%) resected patients with locally advanced or advanced stage of NSCLC. Due to the limited life expectancy (5-year survival rate is around 2%), surgery plays a very limited role. However, in selected cases, in patients with good performance status, surgical intervention, even in an advanced stage, might help to improve life expectancy and quality of life. The most frequent situation, where surgery is performed, is the combination of solitary brain metastasis in a T1/T2 tumor [15]. Stage IIIB patients were classified at this stage because of postoperative multifocal disease in a different ipsilateral lobe, according to the last TNM classification [8]. Stage IV patients were operated on because of concomitant single brain or adrenal gland metastasis treated with surgery in the perioperative period. Other possible explanations might include the screening for early lung cancer detection, which is not in use in our country, and the FDG-PET (18F-fluorodeoxyglucose positron-emission tomography) scan which is not routinely used in our patients.

Most complications are cardiac or pulmonary in origin [16]. In a retrospective study described by Ploeg et al. [17] in 344 resected patients, a total of 341 complications occurred, with 26% incidence of arrhythmia, which consisted mostly of atrial fibrillation as was also shown in our study. This high incidence of arrhythmia is probably due to the large number of pneumonectomies, including extended, as was shown in our case series of 26.88% of the patients. Previous studies demonstrated that arrhythmia was not related to higher mortality and could be successfully managed after lung surgery with antiarrhythmics and anticoagulant therapy to prevent

pulmonary embolism [18]. Postoperative mortality was 1.08%. One 72-year-old man in whom pneumonectomy was performed (IIA/T1bN1M0), with previous history of COPD and chronic heart failure, died on the 7th postoperative day because of pulmonary embolism. The 30-day mortality varies from 2.9 to 12%, which can be explained by the number of extended operations [19].

In our series, we did not find any benefit of adjuvant therapy in overall survival. Five recent trials have investigated adjuvant cisplatin-based chemotherapy [20-24]; only 3 of them have revealed a statistically significant improvement in overall survival [20-22]. The development of prospectively validated molecular markers that are prognostic and predictive would allow better selection of elderly patients with benefit from adjuvant chemotherapy [25].

Long-term survival is also of critical importance in the elderly patients with limited life expectancy. The results of radiotherapy in the elderly are worse compared to surgery, with 5-year survival rates of only 10-20% [26,27]. Our overall 5-year survival of 28.63% is consistent with that reported in similar series over the past decade, with 5-year survival rates of 16-55% [28-30].

Our data suggest that age ≥ 70 years should not be a contraindication for NSCLC resection. Surgery is still the only curative therapy for lung cancer. Careful preoperative assessment must be undertaken for every patient concerning respiratory and cardiac status to reduce the risk of morbidity and mortality. The presence of comorbidities (cardiorespiratory in particular) and the extent of resection predict increased operative risk. Pathological stage is the only predictor of long-term survival.

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