ORIGINAL ARTICLE

LONG TERM FOLLOW-UP IN SURGICAL STAGE I NON-SMALL CELL LUNG CANCER – A SINGLE CENTER EXPERIENCE

Carolina Dantas [*], Sara Campos Silva, David Tavares Silva, João Santos Silva, Ana Rita Costa, João Eurico Reis Paulo Calvinho

[1] Pulmonology department, Hospital Santa Marta, Centro Hospitalar Universitário Lisboa Central
[2] Thoracic Surgery department, Hospital Santa Marta, Centro Hospitalar Universitário Lisboa Central

* Corresponding author: carolinadantas91@gmail.com

Abstract

Introduction: *Lung cancer has a high mortality rate with an overall survival of 18% at 5 years. Surgical treatment is the gold standard for early stages and is associated with high rates of resolution with a 5-year survival of 80% reported in large studies.*

Purpose: *To determinethe survival of patients with non-small cell lung cancer (NSCLC) in stage IA (T1N0M0) undergoing surgical treatment with curative intent in our center.*

Methods: *: We performed a retrospective review of the clinical records of all patients with pathological stage T1a-c N0 (stage I) who underwent thoracic surgery with curative intent from 2010 and 2017 in our center. Overall survival and lung cancer-specific survival was estimated by the Kaplan-Meier method.*

Results:*87 patients (54 men and 33 women) with a median age of 66 years (range 36 to 83 years) were included. Lobectomy with systematic lymph node dissection was performed in 67 patients (77%). Adenocarcinoma was the predominant histological subtype (n=69; 79%). Overall survival at 5th years was 86,7%. Patients submitted to limited resection (segmentectomy or wedge resection) had lower overall survival compared to those submitted to lobectomy (66,4% vs 88,7%; p=0.008).*

Conclusions: *Our results show a high 5-year overall survival rate, in agreement with results from larger series studies. Lung cancer screening, although not yet widely implemented, has been shown to reduce mortality associated with lung cancer. These results reinforce the importance of screening programs for specific populations in order to identify patients in early stages and improve overall survival.*

INTRODUCTION

Worldwide, lung cancer ranks for the leading cause of cancer-related death among men and women, with non-small cell lung cancer (NSCLC) accounting for 84% of all types of lung cancer [1,2]. The most recent European projections show that, unlike most cancers, the trend in the incidence of lung cancer will rise especially in women[3]. Cigarette smoking is thought to be causal in 85 to 90% of all lung cancer, being crucial the promotion of smoking cessation[4]. It is essential to implement integrated primary and secondary prevention strategies. The clinical outcome for NSCLC is directly related to stage at the time of diagnosis. Based on the 8th edition of TNM classification for lung cancer 5-year survival using clinical staging ranges from 92% (stage IA1) to no survival (stage IVB)[5]. Despite advances in therapy, five-year survival rate is approximately 18% for all types of lung cancer, and for NSCLC is estimated to be 23% [6]. In the short term, awareness for smoking cessation and screening in high-risk individuals (smokers and former smokers) is the strategy that will have

the greatest impact in reducing tobacco-related mortalityADDIN BEC[3,6,7]. Results from screening clinical trials with low-dose computed tomography (LDCT) for selected patients are promising, with a remarkable 88% 10-year survival among patients with stage I lung cancer in the International Early Lung Cancer Action Program screening study[8].

Stage I NSCLC includes patients with tumors with 3cm or less in greatest dimension, surrounded by lung or visceral pleura without invading it, and no progression into the main bronchus[5]. For resectable disease in patients with low cardiopulmonary risk, complete surgical resection with lobectomy and systematic lymph node dissection remains the gold standard. The purpose of this study was to review our experience in patients who underwent surgical resection for stage I NSCLC.

MATERIAL AND METHODS

We retrospectively reviewed the clinical records of all patients who underwent surgical resection of NSCLC with tumors ≤ 3cm from January 2010 through December 2017 (7 years). Neuroendocrine tumors were excluded. We analyzed the medical records of each patient regarding age and sex, smoking habits, histology, tumor diameter, postsurgical stage, extent of pulmonary resection and overall survival.

Continuous variables are expressed as mean/median and standard deviation/ interquartile range (IQR), using T-student or Mann-Whitney-U-Test for its comparison. Categorical variables are described as percentages and compared using Fisher's exact test. All p-values are two-sided unless otherwise indicated. In all analysis p-values less than 0.05 were considered statistically significant. Survival analysis was performed using the Kaplan-Meier method.

RESULTS

In this study 87 patients were included (54 men and 33 women) with a mean age of 66 years (range 36 to 83 years). History of tobacco exposure was present in 88,5% of patients. Patients' characteristics are described in Table 1.

A curative lung resection (R0) was achieved in every patient. Lobectomy was performed in 67 patients (77%), segmentectomy in 10 patients (11,5%), wedge resection in 6 patients (6,9%) and bilobectomy in 4 patients (4,6%). Mediastinal lymph node dissection was completed in 85 patients (97,7%).

Tumor histologic characterization showed mostly adenocarcinomas (n=69; 79,3%), but also squamous cell carcinomas (n=16; 18,4%) and large cell carcinomas (n=2; 2,3%).

The tumor size was ≤1cm in 57,5% of cases; >1cm and ≤2cm in 40,2%; and >2cm and ≤3cm in 2,3%. There were no operative deaths.

At data capture for this study 10 (11,5%) of the 87 patients had died. In half of the patients, disease relapse was the cause of death (n=5; 50,0%). Other causes were stroke (n=2; 20,0%), pneumonia (n=1; 10,0%), cholangiocarcinoma (n=1; 10,0%) and hypovolemic shock (n=1; 10,0%). Mean follow-up time was 52 months (range 11-115 months). Disease specific mortality rate was 5,7%.

Patients were divided into two groups for comparison by the type of surgical procedure. The formal resection group (included lobectomy and bilobectomy) included 71 patients (81,6%). The sublobar resection group (underwent either wedge resection or segmentectomy) included the

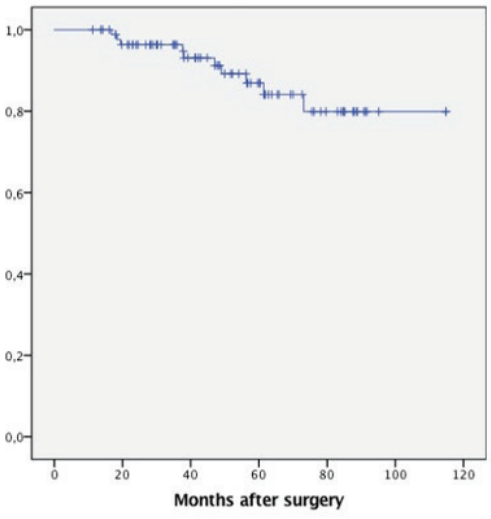

Figure 1 *Overall survival for patients who underwent thoracic surgery for stage I NSCLC.*

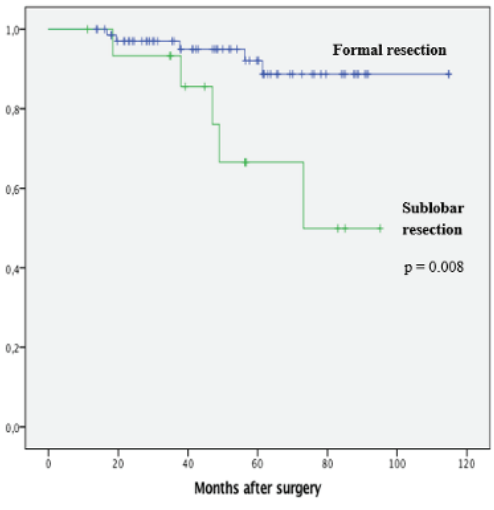

Figure 2 *Overall survival for patients who underwent formal resection (blue line) compared with patients who underwent sublobar resection (green line). Five-year survival for the formal group was 88,7% versus 66,4% for the lobar group (p=0,008).*

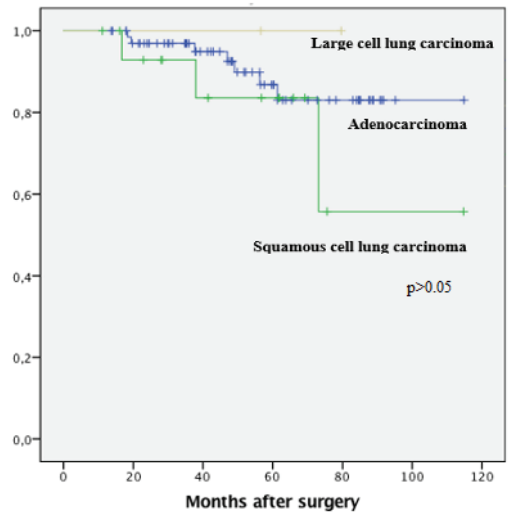

Figure 3 *Overall survival for patients according to the histological subtype (p>0.005; large cell carcinoma grey line; adenocarcinoma blue line; squamous cell lung carcinoma green line).*

remaining 16 patients (18,4%). Patients' characteristics are detailed in Table 2. There was a significantly lower number of deaths in the formal group resection (7,0% vs 31,3%; p= 0,016). Death caused by disease progression occurred in 2 patients in the formal resection group and in 3 patients from the sublobar resection cohort.

The overall 5-year survival was 86,9% (figure 1). Sub-analysis by group showed a significantly lower 5-year survival of the sublobar resection group when compared to the formal resection cohort (66,4% vs 88,7%, log rank testing Mantel-Cox p=0.008) (figure 2).

There were no differences in survival concerning to histological subtype (p>0,05; figure 3).

Regarding surgical technique, video-assisted thoracoscopic surgery (VATS) was performed in 42 patients (48,3%) and thoracotomy in 45 patients (51,7%). When comparing both techniquesaccording to 5-year survival rates, no significant differences were found (79,8% for VATS versus 80,5% for thoracotomy, log rank testing Mantel-Cox p=0.512).

DISCUSSION

Surgical intervention remains the gold standard for early-stage lung cancer. In a recent study conducted by Lu et al., the average of localized stage cancer was 18,8%, with an increasing trend from 16,6% in 1988 to 23,6% in 2015[9]. With the rising number of individuals diagnosed in early stages, it is important to define the most appropriate and effective treatment strategies.

In a retrospective analysis of our results, and according to the current recommendations, the majority of patients

Table 1 **Patients characteristics**

Patients characteristics (n=87)	n	%
Gender		
Male	54	62,1
Gender	33	37,9
Age (years) mean (SD)	66 (±10)	
Tobacco exposure		
Current smokers	56	64,4
Former smokers	21	24,1
Non smokers	10	11,5
Size of the tumor (T)		
T1a (≤1cm)	50	57,5
T1b (>1cm ≤2cm)	35	40,2
T1c (>2cm ≤3cm)	2	2,3
Surgical procedure		
Lobectomy	67	77
Bilobectomy	4	4,6
Wedge resection	6	6,9
Segmentectomy	10	11,5
VATS	45	51,7
Thoracotomy	42	48,3
Mediastinal lymph node dissection	85	97,7
Histological type		
Adenocarcinoma	69	79,3
Squamous cell carcinoma	16	18,4
Large Cells lung cancer	2	2,3

Table 2 **Group comparison by surgical procedure**

	Formal resection (n=71)	Sublobar resection (n=16)	p-value
Age (years) mean (SD)	64 (11) min 36; máx 82	69 (9) min 50; máx 83	p=0,16
Histological type			
Adenocarcinoma	58 (81,7%)	11 (68,8%)	
Squamous cell carcinoma	12 (16,9%)	4 (25,0%)	
Large cell carcinoma	1 (1,4%)	1 (6,3%)	
Deaths	5 (7,0%)	5 (31,3%)	p<0,05
Causes of death			
Disease relapse	2 (2,8%)	3 (18,8%)	
Stroke	1 (1,4%)	1 (6,3%)	
Pneumonia	0 (0,0%)	1 (6,3%)	
Cholangiocarcinoma	1 (1,4%)	0 (0,0%)	
Hemorrhagic shock	1 (1,4%)	0 (0,0%)	

was submitted to formal resection (lobectomy/bilobectomy in 81,6% of cases). Only a minority underwent sublobar resection (18,4%) due to significant comorbidities, lung function prohibited for lobectomy or previous surgically treated lung cancer.We observed an inferior 5-year overall survival for the sublobar resection group (66,4% versus 88,7%, p=0.008), which is in accordance with other series that show superiority of the lobectomy approach[10]. It is important to note that in this study we chose to include theanatomical segmentectomies and the non-anatomical wedge resections inthe sublobar resection group, due to the reduced number of patients in each procedure. Considering the smaller size of the sublobar resection cohort, these results may be explained by the fact that they were older and had more comorbidities when compared to the group submitted to formal resection. The higher disease-related mortality observed in the sublobar resection cohort (18,8% vs 2,8%) is attributable to 2 cases of wedge resection and 1 case of segmentectomy.

When comparing surgical techniques, we did not find differences in the 5-year survival rates between VATS and toracotomy. Our 5-year overall survival of 86,9% in the total cohort of patients was comparable with the results obtained in larger series reports [11-16]. These results are in accordance to the published data in literature, but also lead to several ongoing topics regarding surgical treatment in stage I lung cancer. Standard therapy for patients with stage I lung cancer is anatomic surgical resection with lobectomy and systematic sampling of mediastinal lymph nodes, mostly based on the Lung Cancer Study Group trial published in 1995. This trial compared lobectomy to sublobar resection (including both segmentectomies and wedge resections). Results showed that the limited resection group had an incidence of local recurrence three times higher(p=0.008), a 30% increase in overall death rate (p=0.08) and a 50% increase in cancer-related death (p=0.09) compared with patients undergoing lobectomy[10]. Sublobar resections, preferably anatomical segmentectomy, or wedge resection, may be appropriate in highly selected patients, as those with limited respiratory reserve or comorbidities that increase the perioperative risk, with peripheral nodules ≤ 2 cm and at least one of the following features: 1) pure adenocarcinoma in situ, 2) C/T ratio 50% or less, or 3) radiologically surveyed long tumor doubling time of 400 days or greater[6].

Despite several single center retrospective studies have been published with disagreeing conclusions about the comparison between sublobar and lobar resections, there has not been another published prospective trial on this topic[7]. Ongoing trials in the USA, France and Japan may prove similar overall survivals in the treatment of stage I lung cancer between lobectomy and segmentectomy[17,18].

The surgical technique approach has also been discussed for years. The safety of VATS was established by 2

phase II trials that were conducted over a decade ago[19]. In a phase III randomized controlled trial (RCT) conducted by Long et al, the safety and reliability of VATS for treatment NSCLC was demonstrated[20]. There has been controversy about the safety regarding the complete lymph node dissection with VATS, but the RCTs have showed that a standard lobectomy with lymph node dissection can be performed by VATS with no inferiority compared to toracotomy[21].

Globally, stage I NSCLC has excellent survival however most patients are diagnosed in advanced stages of disease. Aside from primary prevention by promoting smoking cessation, the aforementioned results reaffirm the role of lung cancer screening in identifying patients in early stages of disease. Largerandomized trials showed that screening with low dose computed tomography (LDCT) in high risk populations of current or former smokers was associated with a decrease in lung cancer and all-cause mortality[22,23]. In order to have cost-effective screenings it is essential to develop strict algorithms that define the diagnostic and procedure steps that should be ensured when abnormalities are found. Predictive risk models must also be ensured to identify the individuals who benefit most from screening[3].

In conclusion, our results are in line with what will be the trend and the need for health care systems to adapt to the implementation of screening programs for lung cancer and our results are in line with these premises.

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