Sublobar resection in the treatment of elderly patients with early-stage non-small cell lung cancer

Margarida Afonso[1] , Carlos Branco[2] , Tiago Manuel Alfaro[1]

1. Serviço de Pneumologia, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

2. Centro de Cirurgia Cardiotorácica, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

ABSTRACT

Surgical resection is the primary treatment option for early-stage non-small cell lung cancer, lobectomy being considered the standard of care. In elderly patients, physiological characteristics can limit the suitability for surgery and the extent of resection. Sublobar resection (SLR) can be offered as an alternative. The aim of this real-world analysis was to compare lobectomy and SLR in terms of recurrence and survival rates in patients over 70 years of age.

Keywords: Carcinoma, non-small-cell lung/mortality; Carcinoma, non-small-cell lung/surgery; Recurrence; Aged; Aged, 80 and over.

The incidence of non-small cell lung cancer (NSCLC) increases with age, 40% of cases occurring in patients over 70 years of age. For early-stage disease, surgical resection is the primary option, lobectomy being considered the standard of care. According to the National Comprehensive Cancer Network (NCCN) guidelines, sublobar resection (SLR) is appropriate in cases of reduced pulmonary reserve or major comorbidities and smaller tumors (< 2 cm).[1] Notably, recommendations for lobectomy are based on only one randomized controlled trial, conducted by the Lung Cancer Study Group, which showed that, in comparison with lobectomy, SLR resulted in a 3-fold increase in local recurrence, a 30% increase in overall mortality, and a 50% increase in cancer-related mortality.[2] In elderly patients, physiological limitations and comorbidities can limit surgical eligibility and the extent of resection. Retrospective studies have produced conflicting results regarding the benefits of lobectomy, although only a few have focused on the elderly. Advanced age has been associated with higher morbidity and mortality after lobectomy. In older patients, the risk of death from comorbidities can exceed that of death from cancer.[3] The greater parenchymal preservation in limited resection can challenge the gains achieved in lobectomy.[4] However, questions remain regarding recurrence and survival. In this study, we aimed to compare SLR and lobectomy in patients over 70 years of age with early-stage (stage I or II) NSCLC in a real-life context. We hypothesized that limited resection would produce outcomes similar to those obtained with lobectomy.

We retrospectively studied all patients over 70 years of age undergoing curative lung resection for NSCLC between January of 2012 and December of 2017. Surgery was performed in the thoracic surgery department of a university hospital, and treatment plans were discussed in multidisciplinary meetings. After surgery, all patients were followed at the same hospital. We excluded patients submitted to neoadjuvant treatment because that could indicate a more advanced clinical stage (≥ stage II), which would make them unsuitable candidates for SLR. Patients were divided into groups by the type of procedure they had undergone: SLR and lobectomy.

We reviewed clinical records to collect demographic data, as well as data regarding smoking status; performance status, as determined with the Eastern Cooperative Oncology Group (ECOG) scale; comorbidities, as determined with the Charlson comorbidity index (CCI); lung function, including FVC, FEV_1, and DLCO (all as percentages of the predicted value), as well as the FEV_1/FVC ratio; preoperative blood test results; histology findings; clinical staging; resected lymph nodes (LN); margin status; length of hospital stay; postoperative complications, in the immediate postoperative period and within the first 30 days, as determined with the Clavien-Dindo classification; time to recurrence; and overall survival (OS). For the calculation of the CCI, lung cancer was not considered a comorbidity. Staging was reviewed according to the 8th edition of the International Association for the Study of Lung Cancer tumor-node-metastasis classification of malignant tumors. For each patient, the time to recurrence and the OS were both calculated in months. The time to recurrence was defined as the time from surgery to recurrence, whereas the OS was defined as the time from surgery to death. Data related to patients who did not experience recurrence or die during the study period were censored at the end of the study.

The statistical analysis was performed with the Stata statistical software package, version 13 (StataCorp LP, College Station, TX, USA). Continuous variables were characterized with measures of central tendency (mean or median) and dispersion (standard deviation or interquartile range), according to the normality of the data, as determined with the Shapiro-Wilk test. Categorical

variables were characterized as absolute and relative frequencies. Intergroup differences in categorical variables were evaluated with Student's t-tests for independent variables or Wilcoxon rank-sum tests, according to the normality of the data. For comparisons among groups, ANOVA or the Kruskal-Wallis test was used. Relationships between categorical variables were tested by using chi-square tests. A two-tailed $p < 0.05$ was considered significant.

For the analysis of recurrence-free survival and OS, we calculated estimated values for postoperative months 12, 24, 36, 48, and 60. A univariate analysis was performed by using log-rank tests for dichotomized variables, including demographic characteristics, blood test results, lung function parameters, the ECOG performance status score, the CCI, histology findings, clinical stage, length of hospital stay, and complications. In a multivariate analysis, factors showing a $p < 0.25$ were used in order to construct an initial Cox proportional hazard model, after which a step-down procedure was used in order to select predictors with a $p < 0.05$.

A total of 72 patients were included: 18 (25.0%) were in the SLR group (all 18 underwent wedge resection); and 54 (75.0%) were in the lobectomy group. The choice of wedge resection over segmentectomy was based on the experience at the hospital. Table 1 shows the characteristics of the sample as a whole and of each group. With the exception of lung function, which was slightly worse in the SLR group, there were no significant differences between the two groups.

The mean age of the patients was 78.4 years. Of the 72 patients evaluated, 49 (68.1%) were male, 38 (52.8%) were never smokers, and 70 (97.2%) had an ECOG performance status score of 0 or 1. The most common histological diagnosis was adenocarcinoma. The SLR and lobectomy groups were identical in terms of comorbidities, with a median CCI of 5 (range, 4-8) in both groups, as well as in terms of the mean tumor size and the tumor location. The clinical stage was determined to be IA1 in 26 patients (36.1%), IA2 in 4 (5.6%), IB in 36 (50.0%), IIA in 4 (5.6%), and IIB in 2 (2.8%).

The number of LNs resected was higher in the lobectomy group than in the SLR group (15.6 ± 11.0 vs. 7.4 ± 7.0; $p = 0.005$). Pleural invasion was observed in 28 cases (38.9%) overall, being more common in the lobectomy group, occurring in 23 (42.6%) of the 54 patients in that group, compared with only 5 (27.8%) of the 18 patients in the SLR group, although the difference was not significant. Negative margins were achieved in all cases. The mean hospital stay (in days) was shorter in the SLR group (6.7 ± 3.3 vs. 8.0 ± 3.5), although that difference was also not significant.

Surgical complications in the immediate postoperative period were reported in 18 (25%) of the 72 cases evaluated, 14 complications occurring in the lobectomy group and 4 occurring in the SLR group. Of those 18 complications, 17 were categorized as Clavien-Dindo

grade I, the remaining complication (nosocomial pneumonia requiring antibiotic therapy, in an SLR group patient) being categorized as Clavien-Dindo grade II. The SLR group patient with pneumonia died after discharge (on postoperative day 10). One lobectomy group patient developed a late complication (residual pleural effusion).

In the sample as a whole, the mean follow-up period was 33.5 ± 24.3 months, being 35.5 ± 24.3 months in the SLR group and 32.9 ± 22.0 months in the lobectomy group ($p > 0.05$). The recurrence rate was lower in the SLR group than in the lobectomy group, although the difference was not significant ($p = 0.12$). In the univariate analysis, a platelet density $> 200 \times 10^9/L$, pleural invasion, and a tumor stage > I were found to be significant predictors of recurrence and mortality. In the multivariate analysis, only pleural invasion and platelet density retained their significance. Only a tumor stage > I and pleural invasion were found to be significant predictors of OS in the univariate and multivariate analyses. Although recurrence was a strong predictor of mortality, it was not included in the model, because it was considered part of the causal pathway. Notably, SLR was not associated with a higher risk of recurrence or mortality. The results from the recurrence and survival analyses are reported in Table 2.

The main finding of our study was that, among older patients with early-stage NSCLC, the recurrence and mortality rates observed after SLR were similar to those observed after lobectomy. The length of hospital stay and the rate of postoperative complications were slightly better among the patients undergoing SLR. These results are relevant, because a less invasive approach may be preferable in older patients with NSCLC if it minimizes postoperative mortality and recurrence. Our conclusions are limited by the small size of the sample and retrospective nature. Because this was a retrospective study, it is possible that there was a selection bias. However, it mirrors real-world practice.

Our results complement those obtained by Mery et al.,[5] who showed that the benefits of lobectomy do not extend to patients over 71 years of age.[5] In contrast, Razi et al.[6] found that, in patients over 75 years of age with stage IA NSCLC, cancer-specific survival and OS were lower after wedge resection than after segmentectomy or lobectomy. Nevertheless, the 5-year cancer-specific survival rate was similar among the three groups.

Some aspects of our findings merit special considerations. Having a stage II tumor was found to be associated with higher mortality, with an adjusted hazard ratio (HR) of 4.96 (95% CI: 1.20-24.08). That corresponds to the worse prognosis associated with tumors ≥ 4 cm (stage cT2b).[7] However, the tumor characteristics (histology, size, and location) and tumor stage were equivalent between the two groups, none of those variables being prognostic. Although the NCCN recommends that the use SLR be limited to tumors ≤ 2 cm (stage IA1 or IA2),[1] SLR was performed for larger tumors, with no apparent impact on outcomes,

Table 1. Characteristics of elderly patients with early-stage non-small cell lung cancer, by type of surgical procedure performed.[a]

Characteristic	SLR (n = 18)	Lobectomy (n = 54)	Total (n = 72)	p
Male	14 (77.8)	35 (64.8)	49 (68.1)	NS
Mean age, years	77.2 ± 2.8	78.9 ± 3.2	78.4 ± 3.2	NS
Smoking status				
Never smoker	8 (44.4)	30 (55.6)	38 (52.8)	
Former smoker	8(44.4)	20 (37.0)	28 (38.9)	NS
Current smoker	2 (11.1)	4(7.4)	6 (8.3)	
ECOG performance status score				
0	9 (50.0)	30 (55.6)	39 (54.1)	
1	8 (44.4)	23 (42.6)	31 (43.0)	NS
2	1 (5.6)	1 (1.9)	2 (2.8)	
Charlson comorbidity index	4.9 ± 1.1	4.9 ± 0.7	4.9 ± 0.8	NS
Lung function parameters				
FEV_1, % of predicted	79.1 ± 25.5	103.2 ± 29.1	98.0 ± 29.9	< 0.01
FVC, % of predicted	94.7 ± 22.4	106.6 ± 26.3	104.0 ± 25.8	NS
FEV_1/FVC ratio	64.4 ± 10.6	79.2 ± 16.8	76.0 ± 16.7	< 0.01
Single-breath DLCO, % of predicted	66.3 ± 17.7	75.5 ± 15.9	73.6 ± 16.5	NS
Preoperative blood test results				
BUN, mg/dL	25.1 ± 12.7	20.1 ± 7.6	21.4 ± 9.3	NS
Creatinine, mg/dL	1.07 ± 0.42	0.95 ± 0.44	0.98 ± 0.43	NS
Albumin, g/dL	4.2 ± 0.3	4.3 ± 0.4	4.3 ± 0.4	NS
LDH (U/L)	216.0 ± 63.3	241.8 ± 107.8	235.3 ± 98.6	NS
CRP (U/L)	0.61 ± 0.83	0.69 ± 0.88	0.66 ± 0.86	NS
Leukocyte density, g/L	7.8 ± 2.8	7.2 ± 2.4	7.3 ± 2.5	NS
Hemoglobin, g/dL	13.5 ± 1.5	13.4 ± 1.5	13.4 ± 1.5	NS
Platelet density, g/L	225.0 ± 92.7	209.2 ± 54.2	213.2 ± 65.5	NS
Tumor size, mm	20.6 ± 12.6	23.7 ± 9.9	22.9 ± 10.6	NS
Tumor location				
Right upper lobe	6 (33.3)	14 (25.9)	20 (27.8)	
Right middle lobe	2 (11.1)	2 (3.7)	4 (5.6)	
Right lower lobe	2 (11.1)	12 (22.2)	14 (19.4)	NS
Left upper lobe	4 (22.2)	12 (22.2)	16 (22.2)	
Left lower lobe	4 (22.2)	14 (25.9)	18 (25.0)	
Histology				
Adenocarcinoma	9 (50.0)	44 (81.5)	53 (73.6)	
Squamous cell carcinoma	4 (22.2)	4 (7.4)	8 (11.1)	
Adenosquamous carcinoma	2 (11.1)	4 (7.4)	6 (8.3)	
Pleomorphic carcinoma	2 (11.1)	1 (1.9)	3 (4.2)	NS
Sarcomatoid carcinoma	0	1 (1.9)	1 (1.4)	
Combined tumor type	1 (5.6)	0	1 (1.4)	
Clinical stage				
IA1	4 (22.2)	3 (5.6)	7 (9.7)	
IA2	6 (33.3)	22 (40.7)	28 (38.9)	
IA3	5 (27.8)	20 (37.0)	25 (34.7)	NS
IB	3 (16.7)	5 (9.3)	8 (11.1)	
IIA	0	4 (7.4)	4 (5.6)	
Number of lymph nodes	7.4 ± 7.0	15.6 ± 11.0	13.6 ± 11.0	< 0.05
Pleural invasion	5 (27.8)	23 (42.6)	28 (38.9)	NS
Hospital stay, days	6.7 ± 3.3	8.0 ± 3.5	7.7 ± 3.5	NS
Complications rate	4 (22.2)	14 (25.9)	18 (25.0)	NS

SLR: sublobar resection; NS: nonsignificant; ECOG: Eastern Cooperative Oncology Group; BUN: blood urea nitrogen; LDH: lactate dehydrogenase; and CRP: C-reactive protein. [a]Values expressed as n (%) or mean ± SD.

Table 2. Univariate and multivariate analyses of dichotomized variables to identify predictors of recurrence, mortality, and survival.

Variable	Univariate analysis		Multivariate analysis	
	Recurrence	Mortality	Recurrence	Survival
	p	p	p	p
Male gender	0.94	0.24		
Age ≥ 80 years	0.48	0.56		
Any smoking history	0.75	0.59		
Married	0.11	0.57		
ECOG performance status score > 0	0.46	0.79		
Charlson comorbidity index > 4	0.90	0.36		
FVC < 80% of the predicted value	0.85	0.17		
BUN > 21 mg/dL	0.29	0.21		
Albumin < 4.2 g/dL	0.07	0.08		
Hb < 12 g/dL	0.43	0.74		
Platelet density > 200 g/L	0.03	0.92	0.04	
Tumor size > 20 mm	0.20	0.46		
Tumor located in the right lung	0.11	0.09		
Tumor stage > I	< 0.01	0.03		0.05
SLR	0.12	0.31		
≥ 10 lymph nodes resected	0.62	0.58		
Pleural invasion	< 0.01	< 0.01	0.01	< 0.01
Postoperative complications	0.24	0.37		

ECOG: Eastern Cooperative Oncology Group; BUN: blood urea nitrogen; Hb: hemoglobin; and SLR: sublobar resection.

in our sample. As shown by Harada et al.,[8] SLR may reduce the lung cancer-induced loss of lung function, thus possibly improving survival. In our patient sample, the predictive value of pleural invasion was confirmed; we found that pleural invasion was associated with higher recurrence rates (adjusted HR = 4.67; 95% CI: 1.46-14.98) and lower survival rates (adjusted HR = 3.81; 95% CI: 1.44-10.12). Although a platelet density > 200 g/L has been associated with a risk of disease progression after surgical treatment of NSCLC,[9] further validation is needed.

Surgical margins and LN sampling during SLR warrant discussion. Although the objective of SLR, as defined by the NCCN, should be to achieve surgical margins ≥ 2 cm or that are greater than the size of the nodule,[1] detailed measures were not were not available in the pathology reports for the cases evaluated in the present study. As expected, the number of LNs resected was significantly higher among our lobectomy group patients (p = 0.041), although it did not correlate with recurrence or survival. Because we analyzed the number of LNs but not the number of stations, we cannot determine whether the NCCN recommendation to remove LNs from at least three stations, always including station 7, was followed. Less invasive procedures have been associated with postoperative benefits such as shorter hospital stays and fewer complications.[10] We identified such benefits in our patient sample, which could be explained, in part, by the fact that all of the procedures were performed with an open approach.

Preoperative exclusion of patients with lower lung reserve and more comorbidities, as recommended in the European Respiratory Society/European Society of Thoracic Surgeons guidelines on fitness for radical therapy,[11] should be considered. The fact that those guidelines were followed at the facility under study could explain the lack of any significant impact of those variables in the present study. In our sample, a case-by-case multidisciplinary discussion resulted in a higher proportion of patients being selected for lobectomy than for SLR (75% vs. 25%). This can be interpreted as reflecting the fact that lobectomy is the current standard of care, SLR being a compromise between lobectomy and nonsurgical treatment. However, on the basis of the data available, we cannot draw a definitive conclusion regarding whether SLR was the procedure of choice or was chosen as a compromise solution. Nevertheless, in elderly patients with early-stage NSCLC, the results achieved with SLR appear to be equivalent to those achieved with lobectomy.

REFERENCES

1. National Comprehensive Cancer Network (NCCN) [homepage on the Internet]. Brussels: NCCN; c2019 [cited 2019 Jan 18]. Non-small cell lung cancer (version 3.2019). Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
2. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg. 1995;60(3):615-623. https://doi.org/10.1016/0003-4975(95)00537-U
3. Guerra M, Neves P, Miranda J. Surgical treatment of non-small-cell lung cancer in octogenarians. Interact Cardiovasc Thorac Surg.

2013;16(5):673-680. https://doi.org/10.1093/icvts/ivt020

4. Groth SS, Rueth NM, Hodges JS, Habermann EB, Andrade RS, D'Cunha J, et al. Conditional cancer-specific versus cardiovascular-specific survival after lobectomy for stage I non-small cell lung cancer. Ann Thorac Surg. 2010;90(2):375-382. https://doi.org/10.1016/j.athoracsur.2010.04.100

5. Mery CM, Pappas AN, Bueno R, Colson YL, Linden P, Sugarbaker DJ, et al. Similar long-term survival of elderly patients with non-small cell lung cancer treated with lobectomy or wedge resection within the surveillance, epidemiology, and end results database. Chest. 2005;128(1):237-245. https://doi.org/10.1378/chest.128.1.237

6. Razi SS, John MM, Sainathan S, Stavropoulos C. Sublobar resection is equivalent to lobectomy for T1a non-small cell lung cancer in the elderly: a Surveillance, Epidemiology, and End Results database analysis. J Surg Res. 2016;200(2):683-689. https://doi.org/10.1016/j.jss.2015.08.045

7. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93-99. https://doi.org/10.3322/caac.21388

8. Harada H, Okada M, Sakamoto T, Matsuoka H, Tsubota N. Functional advantage after radical segmentectomy versus lobectomy for lung cancer. Ann Thorac Surg. 2005;80(6):2041-2045. https://doi.org/10.1016/j.athoracsur.2005.06.010

9. Yu D, Liu B, Zhang L, DU K. Platelet count predicts prognosis in operable non-small cell lung cancer. Exp Ther Med. 2013;5(5):1351-1354. https://doi.org/10.3892/etm.2013.1003

10. Kilic A, Schuchert MJ, Pettiford BL, Pennathur A, Landreneau JR, Landreneau JP, et al. Anatomic segmentectomy for stage I non-small cell lung cancer in the elderly. Ann Thorac Surg. 2009;87(6):1662-1668. https://doi.org/10.1016/j.athoracsur.2009.02.097

11. Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculier JP, Varela G, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy) [published correction appears in Eur Respir J. 2009 Sep;34(3):782]. Eur Respir J. 2009;34(1):17-41. https://doi.org/10.1183/09031936.00184308