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Early outcome of anatomical lung resection for non-small cell lung cancer in the elderly

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Abstract. – OBJECTIVE: Surgery is the mainstay of early-stage lung cancer treatment. However, since life expectancy is constantly increasing, we wanted to investigate whether this principle also applies to elderly (≥70-year-old) patients.

PATIENTS AND METHODS: We analyzed a prospectively maintained database on anatomical lung resections at our institute. Patients were divided in two groups: <70 years and ≥70 years (elderly). Outcome indicators were postoperative cardiopulmonary complications rate and 30-day readmission rate. Baseline and surgical characteristics were compared by mean of t-test, Mann-Whitney U test, chi2 and Fisher exact tests. Propensity score matching was performed to account for differences between groups in the outcome's analysis.

RESULTS: We selected 241 patients with lung cancer (2017-2021) who underwent anatomical lung resections. Median age was 70.5 (IQR: 64-76). 133 patients (54%) aged 70 and above. Patients and surgical characteristics (comorbidities, lung function, performance status, type and extension of lung resection and surgical approach) were similar among groups, except for atrial fibrillation (p=0.01) and previous cancer history (p<0.0001) which were more frequent in the elderly group. Non-elderly patients were more frequently active smokers (p<0.0001). Cardiopulmonary complications rate was 23%, 30-day readmission rate was 12.6%. We did not observe any significant difference in all the short-term outcome indicators between the elderly and the younger counterpart. Particularly, complications rate (p=0.91) and 30-day readmission (p=0.84) did not differ between groups.

CONCLUSIONS: In our series, short-term outcomes are not compromised in elderly patients. The evolution in surgical strategy and expertise contribute to offer surgical resection with curative intent for lung cancer to a large spectrum of patients.

Key Words:
MiRNA-106, Pediatric osteosarcoma, PI3K/AKT signaling pathway.

Introduction

Non-small cell lung cancer (NSCLC) remains the most common cause of cancer-related death worldwide[1]. Recent epidemiological statistics, set the median age at diagnosis at 70 years in United States[1], defining this cancer as a disease of the elderly[2]. Anatomical lung resection is the standard of care in resectable cancers[3]. However, with advancing age, patients are more likely to have multiple medical comorbidities and worsening performance status, thus surgical indication might be questionable. Indeed, preoperative workup includes cardiac and lung function evaluation[4], however, even though age has been identified as independent risk factor for morbidity and mortality after lung resection[5], it is not considered an absolute contraindication to surgery. In other words, biological age seems to be more important than chronological age in evaluating risks and benefits of surgery for lung cancer.

In line with lung cancer epidemiology, surgical units also find themselves having to consider and treat a progressively larger number of elderly patients. While it is certainly true that age is a drawback, improved surgical techniques, attention to patient's selection, and collegiality of the specialties involved should have had a positive impact on surgical outcomes.

With our study we wanted to analyze the outcome, during the recent years, of the elderly population compared to the younger counterpart. Particularly, we focused on the early surgical outcomes defined as perioperative complications and 30-day readmission rate, to highlights differences and possible pitfalls of care.

Patients and Methods

Patients' Selection

This is a retrospective analysis of prospectively maintained database on anatomical lung resec-

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tion performed at our institution. We screened it for consecutive surgical resections performed for pathologically proven NSCLC between January 2017 and March 2021. Demographics, clinico-pathological characteristics, postoperative course, details of medical and surgical treatments and 30-day readmission rate were extracted. The study was approved by the Cantonal Ethics Committee. We identified patients who underwent anatomical lung resections including pneumonectomies, lobectomies, bilobectomies and segmentectomies. For the purpose of the study, we included only patients with diagnosis of non-small cell lung cancer at final pathological examination. All operations were performed by board certified thoracic surgeons either through three ports thoracoscopy (VATS), muscle sparing thoracotomy or robotic-assisted thoracoscopic surgery (RATS). Patients were selected for operation according to current functional guidelines and after discussion during multidisciplinary tumor board meetings[6]. Post-surgical care provided initial monitoring in high dependency unit and subsequent transfer to a dedicated ward when clinically indicated. Standard pathways of care included patient-controlled analgesia, early mobilization and respiratory physiotherapy. Patients were discharged home or to rehabilitation facilities, after clinical evaluation and when the final assessment included evaluation of social support and eventual nursing care needs.

Variables Definition

Baseline patients' characteristics included preoperative pulmonary function [Forced Expiratory Volume in 1 second (FEV1) and Diffusion Capacity of the Lung for Carbon Monoxide (DLCO)], medical comorbidities, smoking history (current smoker versus former and never smokers), previous history of cancer and ECOG Performance Status (PS). Surgical variables were also collected, including technical approach, conversion rate and extent of resection. Post-operative course variables included drain management, length of stay and in-hospital death.

The main outcomes of the study were: the onset of major cardiopulmonary complications during the postoperative course and the 30-day readmission in hospital rate. Major cardiopulmonary complications were defined according to the ESTS definition. Pneumonia, Adult Respiratory Distress Syndrome (ARDS), atrial arrhythmia, atelectasis needing bronchoscopy, acute pulmonary embolism, acute myocardial infarct, mechanical ventilation >24h, cardiac failure, pulmonary edema, stroke, acute kidney injury and deep vein thrombosis (DVT) were recorded in line with the joint standardization of variable definitions and terminology published in 2015[7].

30-day readmissions in hospital were checked through electronic system and patients telephone interview. The population was divided in two groups (<70 years: non-elderly, ≥70 years: elderly) and tested for variables comparison and association with the outcomes.

Statistical Analysis

Patient-related, surgical variables and outcomes were analyzed and compared in the two groups. Continuous variables were tested for normality with the Shapiro-Wilk test. Normally distributed variables were analyzed using the Student's *t*-test; skewed distributed ones were analyzed with the Mann-Whitney U test. Categorical variables were tested by means of the Fisher's exact test (in case the number of observations was less than 10 in at least one cell) or Chi-squared test.

Statistically significant differences in the characteristics between the two groups were considered as possible confounders and a propensity score matching was used to account for them and adjust the results. Moreover, variables known to influence the onset of cardiopulmonary complications[5] or 30-day readmission rate[8] were included in the propensity score despite their statistical significance at univariable analysis. One-to-one matching using nearest neighbor matching method was performed. Pairs on the propensity score logit were matched within a range of 0.2 standard deviation with calipers 0.2[9].

The level of significance was set at 0.05, all statistical analysis were performed using STATA software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Results

241 patients were included in the analysis. Median age was 70.5 years (IQR: 64-76) with 133 (54%) patients aging 70 years or above. We performed a total of 207 lobectomies, 7 bilobectomies, 23 segmentectomies and 4 pneumonectomies, including 37 extended resections (chest wall, pericardium, diaphragm, sleeve resections). 178 operations were approached through minimally invasive surgery with a conversion rate

of 22%. Histology was adenocarcinoma in 168 (70%) of cases, with a total of 82 (34%) of early stages (IA-IB). 55 patients (22.8%) experienced at least one cardiopulmonary complication, in–hospital mortality rate was 1.2% and the 30-day readmission rate was 12.6%. Table I shows the details of patients and surgical baseline characteristics, and the overall outcomes.

Non-elderly group and elderly group showed substantial homogeneity of characteristics with the exception of smoking habits, with more active smoker in the non-elderly group, atrial fibrillation and cancer history, which were more frequent in the elderly group.

We did not observe statistically significant differences in the outcomes in the two group. Neither the cardiopulmonary complications rate, nor the 30-day readmission rate differed between elderly and non-elderly. Tables II shows details of the univariable analysis.

Propensity score matching analysis created 108 matched pairs. Table III showed the comparison between the two groups with all the included variables. No difference in the outcomes was found after adjusting for confounders (average treatment effect for cardiopulmonary complications rate: p= 0.57; average treatment effect for 30-day readmission rate: p= 0.91) (Table IV).

Table I. Patients baseline characteristics, surgical and oncological outcomes.

Variables (population: n= 241)	
Age (median, years)	70.5 (IQR: 64-76)
Pre-op FEV1 (mean)	85 (SD: 19.5)
Pre-op DLCO (median)	71 (IQR: 59-84)
Smoking history	
Current	111 (46)
Former	99 (41)
Never	29 (12)
BMI (median)	25.3 (IQR: 22.2-28.4)
Lung cancer stage	
IA	101 (42)
IB	41 (17)
IIA	17 (7)
IIB	35 (14.5)
IIIA	36 (15)
IIIB	9 (3.7)
IV	2 (0.8)
Histology	
Adenocarcinoma	171 (71)
Squamous cell carcinoma	45 (18.7)
Typical carcinoid	10 (4.1)
Other	15 (6.2)
Air leak duration (median, days)	1 (IQR: 0-3)
Intercostal tube duration (median, days)	3 (IQR: 2-5)
Length of stay (median, days)	6 (IQR: 4-9)
Cardiopulmonary complications (n of patients)	55 (22.8)
Pneumonia (n)	17
ARDS (n)	0
Atrial fibrillation (n)	15
Atelectasis (n)	12
Pulmonary embolism (n)	1
Acute myocardial infarct (n)	0
Initial mechanical ventilation >24h (n)	6
Cardiac failure (n)	0
Pulmonary edema (n)	1
Stroke (n)	1
Acute kidney injury (n)	2
Deep venous thrombosis (n)	0
In-hospital death	3 (1.2)
30-readmission rate*	30 (12.6)

Results are expressed as % unless otherwise specified. FEV1: forced expiratory volume in 1 second; DLCO: diffusion capacity of the lung for carbon monoxide; BMI: body mass index; ARDS: adult respiratory distress syndrome; SD: standard deviation; IQR: interquartile range. (*): % refers to minimally invasive approach.

Table II. Groups' comparison.

Variables	Non-elderly (n = 108, 45%)	Elderly (n = 133, 54%)	*p*-value
Male sex	61 (56.5)	76 (57.1)	0.65
Pre-op FEV1 (mean)	84.5 (SD: 20.1)	86.2 (SD: 19.1)	0.52
Pre-op DLCO (median)	70 (IQR: 57-84)	72 (60-84)	0.62
Smoker	64 (59.2)	47 (35.3)	< 0.0001
BMI (median)	25.6 (IQR: 22.3-28.5)	25.1 (IQR:22.1-28.4)	0.62
Diabetes	16 (14.8)	20 (15)	0.96
Liver disease	8 (7.4)	7 (5.2)	0.49
Atrial fibrillation	2 (1.8)	13 (9.7)	0.01
Hypertension	53 (49)	66 (49.6)	0.93
Coronary artery disease	24 (22.2)	22 (16.5)	0.26
Cerebro-vascular disease	13 (12)	15 (11.2)	0.85
Previous cancer	21 (19.4)	54 (40.6)	< 0.0001
PS ≥2	5 (4.6)	10 (7.5)	0.33
Minimally invasive approach	79 (73.1)	100 (75.1)	0.58
Pleural adhesions	41 (37.9)	38 (28.5)	0.11
Conversion rate*	18 (22.7)	21 (21)	0.74
Systematic lymphadenectomy	99 (91.6)	128 (96.2)	0.34
Pneumonectomy	2 (1.8)	2 (1.5)	0.84
Extended resection	14 (12.9)	23 (17.2)	0.35
Early lung cancer stage	74 (68.5)	85 (63.9)	0.45
Air leak duration (median)	1 (IQR: 0-3)	1 (IQR: 0-2)	0.58
Intercostal tube duration (median)	3 (IQR: 2-5)	3 (IQR: 2-6)	0.74
Discharge with drain	2 (1.8)	5 (3.7)	0.46
Length of stay (median)	6 (IQR: 4-6)	6 (4-9)	0.24
In-hospital death	1 (0.9)	2 (1.5)	0.57
Cardiopulmonary complications	25 (23.1)	30 (22.5)	0.91
30-readmissions	14 (12.9)	16 (12)	0.84

Results are expressed as % unless otherwise specified. FEV1: forced expiratory volume in 1 second; DLCO: diffusion capacity of the lung for carbon monoxide; BMI: body mass index; PS: ECOG performance status; SD: standard deviation; IQR: interquartile range. (*): % refers to minimally invasive approach.

Discussion

In our population we did not observe differences in early outcomes between elderly and non-elderly patients after anatomical lung resection for lung cancer. Even accounting for possible confounders, we could not demonstrate a difference in the considered outcomes. These data are encouraging and demonstrate a different trend from what has been reported in the literature.

Table III. Matched cohort comparison.

Prpensity score matched cohort			
Variables	**Non-elderly (n= 108)**	**Elderly (n= 108)**	***p*-value**
Male sex	64 (59.2)	61 (56.5)	0.53
Pre-op FEV1 (mean)	84.5 (SD: 20.1)	85.5 (SD: 19.7)	0.71
Smoker	64 (59.2.)	63 (58.3)	0.83
Atrial fibrillation	2 (1.8)	2 (1.8)	–
Coronary artery disease	24 (22.2)	17 (15.7)	0.22
Cerebro-vascular disease	13 (12)	13 (12)	–
Previous cancer	21 (19.4)	30 (27.7)	0.06
Minimally invasive approach	79 (73.1)	78 (72.2)	0.45
Extended resection	14 (12.9)	19 (17.6)	0.34
Air leak duration (median)	1 (IQR: 0-3)	1 (IQR: 0-2)	0.69
Cardiopulmonary complications	25 (23.1)	22 (20.4)	0.62
30-readmissions	14 (12.9)	12 (11.1)	0.69

Results are expressed as % unless otherwise specified. FEV1: forced expiratory volume in 1 second; SD: standard deviation; IQR: interquartile range.

Table IV. Results of treatment-effect estimation after propensity score matching (treatment = elderly).

Outcome	Odds ratio	Robust standard error	*p*-value	95% confidence interval
Cardiopulmonary complications	1.03	0.06	0.57	-0.15-0.08
30-day readmission rate	0.99	0.04	0.91	-0.1-0.09

Lung cancer must be considered a disease of the elderly, as the median age at diagnosis has progressively increased over time[10]. It is undisputable that advanced age is largely synonymous of increased number of comorbidities, polytherapy and physiological reduction in performance status and general health[11,12]. Moreover, patients with lung cancer often present cardiovascular comorbidities related to smoking habit and lifestyle. Recent updates in lung cancer treatment guidelines introduce special recommendation for elderly patients with respect of radiotherapy as alternative to surgery for early stage[13]. However, despite advances in systemic treatment with the introduction of target therapies and immunotherapies, and despite favorable results with the use of radiotherapy, many elderly patients do not receive any form of treatment, even for early stages[14]. Surgery remains the gold standard of treatment in resectable disease[3,13]. Scholars[15] come from surgical trials that carry a bias due to population selection, being these patients relatively young. The elderlies are often excluded from clinical trials and under-represented in almost all cancer research[16-18]. They often receive alternative or untested treatments based on the general notion that old patients are incapable of tolerating exigencies of treatment[19].

Along with other clinical characteristics, age is considered a risk factor for both morbidity[5] and 30-day unplanned readmission, with a greater risk of short- and long-term mortality[20]. It is therefore undebatable that we should identify patients at risk and develop measures to avoid the associated adverse outcomes. On the other hand, we cannot ignore the fact that the age of oncologic population is constantly increasing and excluding a priori elderly from radical treatments it is not acceptable.

In our series we included consecutive patients we operated on for non-small cell lung cancer between 2017 and 2021, with a rate of elderly patients of 54%. This represents a real word picture that our thoracic surgery unit face during clinical activity in the last years. All patients were tested in regards of lung function, cardiac function and overall general status. Onco-geriatric assessment was made when indicated by the multidisciplinary team meeting and specifically for patients >70-year-old. Age itself did not represent an absolute contraindication to surgery.

As suggested by international guidelines[13], early-stage lung cancers were approached with minimally invasive surgery. As demonstrated by previous studies[21,22], the outcome of surgery can be improved by video-assisted thoracic surgery (VATS), which has been shown to be superior to thoracotomy in terms of postoperative morbidity, even in octogenarians.

The concept of multispecialty expertise became pivotal when treating elderly patients. The European Association for Cardio-Thoracic Surgery (EACTS) and the European Society of Thoracic Surgeons (ESTS) have proposed recommendations for the structural characteristics of general thoracic surgery specialty to improve short- and long-term outcomes[23]. These recommendations have been recently revised and refined with the publication of the European guidelines on structure and qualification of general thoracic surgery[24]. This European position explore different aspects of the quality of care in thoracic surgery, giving precise definitions. It is important to underline that the core of the unit is always represented by a competent surgical team, but hospital structures and expertise, including intensive care unit, ward, theatres, and diagnostic facilities, play a key role in the correct definition of surgical unit and in ensuring the appropriate level of care.

Effective geriatric assessment is mandatory to stratify risks and benefits of lung cancer treatments. A recent study[25] performed with the data on two randomized trials on advanced lung cancer in elderly patients showed that mini mental state examination scores, performance status and sex, but not chronological age, effectively predicted the prognosis. For surgical population, dedicated geriatric assessment was associated with overall survival values that are similar to outcomes in younger patients in a study conducted by Thomas et al[26]. They also observed that the use of minimally invasive surgery and the performance of systematic lymphadenectomy were also associated with improved long-term survival[26].

Overall, we can speculate that age of patients has been recognized as a potential liability and possible strategies to reduce the impact of this non-modifiable factor has been implemented. Particularly, the use of minimally invasive approach, the proposal of onco-geriatric assessment, the grouping of expertise, including different levels of care, might have had a positive impact on the outcomes.

Our study has some limitations. First, the retrospective design of the study carries an inherent bias. On the other hand, our data reflect the current clinical practice with no selection bias: the analyzed population referred to a consecutive series of patients who have been operated on following the standard guidelines on lung cancer treatment. The study was not designed to assess the long-term results, neither we made a comparison with alternative treatments. The lack of a time-trend on the outcomes only permits common sense considerations about improvements related to technical and facilities improvements.

Conclusions

Our data showed that anatomical lung resections are safe and effective in terms of short-term outcomes in elderly patients. Indication for surgery should not be precluded only on the base of chronological age. However, surgical expertise, multidisciplinary approach and geriatric and oncology specialist evaluation might be essential in selecting adequate candidates.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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