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Early and long-term results of pulmonary resection for non-small-cell lung cancer in patients over 75 years of age: a multi-institutional study

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Abstract

OBJECTIVES: Older lung cancer patients with multiple morbidities are increasingly referred to thoracic surgery departments. The aim of this multicenter study was to analyse the prognostic factors for in-hospital morbidity and mortality and to elucidate the predictors of long-term survival and oncological outcomes.

METHODS: We identified 319 patients aged ≥75 years who underwent intended curative lung resection for lung cancer in three different thoracic surgery departments between January 2000 and December 2010.

RESULTS: Seventy-one patients underwent limited resection, 202 had lobectomy, 16 had bilobectomy and 30 had pneumonectomy. The in-hospital mortality was 6.6%. Chronic renal failure, low respiratory reserve and pneumonectomy were predictors of in-hospital mortality. The mean follow-up time was 3.9 years, ranging from 1 month to 10.4 years. The disease-free survivals at 1, 3 and 5 years were 82, 60 and 47%, respectively. The overall survivals at 1, 3 and 5 years were 86, 59 and 38%, respectively. The long-term overall survival was negatively influenced by pneumonectomy, extended resection, N_{1-2} subgroups and pathological TNM stage.

CONCLUSIONS: Nowadays, we can consider surgery a safe and justifiable option for elderly patients. Careful preoperative work-up and selection are mandatory to gain satisfactory results. Good long-term results were achieved in elderly patients with early stage who underwent lobar or sublobar lung resection. The role of surgery or other alternative therapies, in patients with advanced stages, extensive nodal involvement and/or requiring extensive surgical resection for curative intent, is still unclear and further studies are certainly needed.

Keywords: Lung cancer • Older patients • Thoracic surgery • Lung surgery

INTRODUCTION

It is difficult to define the elderly. In western countries, including Italy, the average age of the general population is increasing [1, 2]. In the 2005 report of the National Italian Institute of Statistics, the mortality rate due to lung cancer is increasing in people aged ≥75 years [2]. Moreover, 14% of patients who die of lung cancer are >80 years [2]. Accordingly, it is anticipated that an increasing number of elderly patients with non-small-cell lung cancer (NSCLC) will be referred to physicians and surgeons in the forthcoming years.

The elderly are a heterogeneous group of patients, but according to the American College of Chest Physician guidelines [3] and the European Respiratory Society/European Society of Thoracic Surgeons recommendations [4], surgery should not be denied based on older age alone. Janssen and Kunst [5] estimated that, in 2050, the life expectancy of people reaching 80 years of age will be 9.16 years for men and 12.65 years for women. In such scenario, tumours may have an important impact on long-term survival and quality of life in older people more than age alone. A still-debated aspect is the long-term benefit of surgery in elderly patients because ageing itself is an independent significant factor affecting survival [6–9].

The aim of this multicenter study was to analyse the prognostic factors for in-hospital morbidity and mortality and to elucidate the predictors of long-term survival and oncological outcomes.

MATERIALS AND METHODS

Data collection

The same data and variables were collected retrospectively from prospectively structured lung cancer databases from three thoracic surgical units. We focused on patients aged ≥75 years who underwent intended curative lung resection for NSCLC between January 2000 and December 2010. We identified 319 such patients, representing 13.8% of the overall lung resections performed during the study period. The long-term follow-up was obtained through examination wherever possible, or by telephone interviews of the patients themselves or of a family member. In the remaining cases, follow-up was obtained from patient's general practitioners or registry offices.

Statistical analysis

Statistics were performed using Statistical Package for Social Science (SPSS) version 11.0 for windows (SPSS, Inc., Chicago, IL, USA).

Continuous variables were reported as mean ± SD, whereas categorical variables were given as percentages. In-hospital risk factors for mortality and morbidity were analysed using a binary logistic regression model. The Cox multivariate regression was used to identify independent prognostic factors for long-term mortality using a stepwise model. The Hosmer–Lemeshow test showed a good overall model fit ($\chi^2 = 6.4$, 4 df, $P = 0.171$).

A *P*-value <0.05 was considered to be statistically significant. Survival analysis was conducted according to the Kaplan–Meier method, and curves were compared by the log-rank test. Survival was reported as an overall survival and a disease-free survival. The starting date for long-term evaluation was on postoperative day 31 or alternatively, the day of discharge if it occurred later. Operative death was excluded from long-term statistical evaluation.

Patients

There were 257 males (80.6%) and 62 females (19.4%). The median age at the time of surgery was 78.1 ± 2.7 years (range 75–89 years). Seventy-one patients were >80 years (22.3%). Preoperative variables and comorbidities are summarized in Table 1. Most of the patients were asymptomatic (79.8%) and lung cancer was an incidental finding in a chest X-ray during medical evaluation for other reasons. Preoperative assessment included careful anamnesis, physical examination, routine blood test, electrocardiogram and spirometry with blood gas analysis. Echocardiography and myocardial scintigraphy were performed if the patient had a history of angina or an abnormal baseline electrocardiogram. If myocardial scintigraphy was positive for ischaemia, a coronary angiography was performed. The CO diffusion capacity and lung perfusion scintiscan were performed in the event of poor pulmonary function (forced expiratory volume in 1 s [FEV1] <60% of the predicted) or when a major resection was planned. The histological diagnosis of tumour was preoperatively obtained by trans-bronchial needle aspiration, brushing or bronchial-alveolar lavage during flexible and/or rigid bronchoscopy, alternatively by transparietal computed tomography (CT)-guided biopsy, in the majority of the patients. After 2005 the clinical staging process started with a total body CT scan followed by positron emission tomography (PET) even in the event of no evidence of lymph nodes enlargement on the CT scan. Before 2005, all patients with enlarged mediastinal lymph nodes on the CT scan (short axis >1 cm) underwent mediastinoscopy to complete clinical staging. The bone scintigraphy was used until the advent of PET. After 2005, only patients who had PET positive mediastinal lymph nodes underwent mediastinoscopy or EBUS/EUS biopsy to complete clinical staging. Twenty-five (7.8%) patients had history of previous pulmonary resection. Induction chemotherapy was used in 5 (1.6%) patients, while induction radiation therapy was used in 1 (0.3%).

Table 1: Preoperative patients profile

Variables	No. of patients
Systemic hypertension	189 (59%)
COPD/asthma	103 (32%)
Vascular disease	62 (19%)
Chronic ischaemic cardiomyopathy	66 (21%)
Heart valvular disease	8 (3%)
Previous CVA/TIA	42 (13%)
Chronic renal failure (creatinine >2 mg/dl)	27 (9%)
FEV1 <60%	86 (27%)
DLCO (% ±DS)	71 ± 31
Diabetes mellitus	29 (9%)
Chronic AF	18 (6%)
Obesity	15 (5%)
Never smoker	42 (13%)
Current smoker	92 (29%)
Former smoker	185 (58%)
Previous lung resection	25 (8%)
>1 Comorbidity	222 (70%)

COPD: chronic obstructing pulmonary disease; CVA: cerebral vascular accident; TIA: transient ischaemic accident; FEV1: forced expiratory volume in 1 s; DLCO: diffusing lung carbon monoxide capacity; AF: atrial fibrillation.

RESULTS

Surgical procedure and adjuvant therapy

The decision between lobar and sublobar resection was based on respiratory function, performance status and comorbidities in every single patient. In general, we were in favour of lobar resection whenever possible. Every effort was made to avoid pneumonectomy, in particular on the right side. The pneumonectomy was offered only to very healthy older patients with good respiratory function and minor comorbidities overall; 211 (66%) patients had a right-sided procedure and 108 (34%) had a left-sided procedure. Seventy-one (22.3%) patients underwent limited resection as segmentectomy or wedge resection, 202 (63.3%) had lobectomy, 16 (5%) had bilobectomy and 30 (9.4%) had pneumonectomy (12 right and 18 left). Two patients who underwent a right upper sleeve lobectomy and a right inferior sleeve lobectomy in the 2007 and 2008 had completion pneumonectomy after 25 and 14 months, respectively. In addition, 31 (9.7%) patients underwent extended resection including

Table 2: Operative results

	No. of patients	Percentage
Surgical procedure		
Segmentectomy/wedge resection	71	22.3
Lobectomy	202	63.3
Bilobectomy	16	5
Pneumonectomy	30	9.4
	Right 12	
	Left 18	
Completion pneumonectomy	2	0.6
Associated procedures		
Extended resection	31	9.7
Chest wall resection	26	8.2
Left atrium resection	5	1.6
Pathological N stage		
N_0	233	73
N_1	68	21.3
N_2	18	5.6
Pathological TNM stage		
Ia	93	29.2
Ib	77	24.1
IIa	60	18.8
IIb	42	13.2
IIIa	38	11.9
IIIb	9	2.8

26 resections of the chest wall and 5 partial resections of the left atrium wall (Table 2). In all patients, lymphadenectomy was done before lung resection. On the right side, lynphadenectomy was defined as the removal of all the 2R, 4R, 7, 8, 9 lymph nodes, on the left side 5, 6, 7, 8, 9 lymph nodes were removed. The 4L station was dissected only in case of high suspicion of neoplastic involvement, if the preoperative medistinoscopy and/or EBUS were negative.

Histology and pathological staging

All patients were restaged using the seventh version of the TNM [10]. Using this classification, 93 (29%) patients were in pathological Stage pIa, 77 (24%) in Stage pIb, 60 (19%) in Stage pIIa, 42 (13%) in Stage pIIb, 38 (12%) in Stage pIIIa and 9 (2.8%) in Stage pIIIb. pN_0 disease was present in 233 (73%) patients, pN_1 disease in 68 (21%) and pN_2 disease in 18 (5.6%; Table 2). A T_3 disease was described in 37 (11.6%) patients and a T_4 disease in 9 (2.8%).

Histological definition was undertaken according to the WHO criteria for the classification of NSCLC [11]. Histological diagnosis showed a prevalence of 137 patients with adenocarcinomas (42.9%) followed by 135 with squamous cell carcinoma (42.3%), 12 with bronchiolar alveolar cell carcinoma (3.8%) and 35 with other tumours (11%) such as carcinoids and large-cell carcinomas.

In-hospital results

The overall in-hospital mortality was 6.6% (21 of the 319 patients). In our series, the in-hospital mortality of septuagenarians (236 patients) and octogenarians (83 patients) were 6.8 and 6.0%, respectively, without statistical significant difference ($P = 0.98$). The in-hospital mortality for pneumonectomy was 23.3% (7 of 30 patients), 5.5% in case of lobectomy/bilobectomy (12 of 218 patients) and 2.8% in case of sublobar resection (2 of 71 patients). The main causes of death were acute respiratory distress syndrome (ARDS) following pneumonia in 8 patients, acute myocardial infarction (AMI) in 7, acute bowel ischaemia in 3 and ARDS with bronchopleural fistula in 3. Low respiratory reserve ($P < 0.0001$), chronic renal failure ($P < 0.01$), pneumonectomy ($P < 0.001$), extended resection ($P < 0.05$), squamous cell carcinoma histology ($P < 0.03$) and pathological stage ($P < 0.04$) were risk factors for in-hospital mortality in a univariate model. At the multivariate analysis, chronic renal failure ($P < 0.004$), low respiratory reserve ($P < 0.009$) and pneumonectomy ($P < 0.0001$) were confirmed as the predictors of in-hospital mortality (Table 3). Overall, postoperative complications occurred in 155 (48.6%) patients; of these, 58 (37.4%) suffered more than one postoperative complication. The major postoperative complications are reported in detail in Table 4. Forty-seven (14.7%) patients developed pulmonary atelectasis and required frequent bronchial aspiration, 45 (14%) had at least one episode of atrial fibrillation, 27 (8.5%) had prolonged air leaks and 7 (2.2%) had postoperative haemothorax requiring surgical revision in 4 cases (1.3%). Prolonged mechanical ventilation or reintubation was required in 18 patients during the postoperative period (5.6%); in 4 cases, a tracheostomy was performed (1.3%). Seventeen (5.3%) patients suffered AMI during the postoperative period, 11 of these patients had a previous history of ischaemic disease (65%). The mean hospital stay was 7.7 ± 3.5 days.

Table 3: Risk factors for in-hospital mortality at the univariate and multivariate regression analyses

Variables	RR	95% CI	*P*-value
Univariate analyses			
Pneumonectomy	5.5	1.9–15.5	0.001
FEV1 <1 l	8.7	1.8–12.9	0.0001
Chronic renal failure	4.2	1.5–12.7	0.01
Extended resection	2.6	1.4–8.7	0.05
Histology (squamous)	3.6	1.5–11.4	0.03
Pathological Stage III	2.8	1.0–7.3	0.04
Multivariate analyses			
Chronic renal failure	4.7	1.6–13.1	0.004
FEV1 <1 l	1.5	1.1–2	0.009
Pneumonectomy	5.6	2.3–13.7	0.0001

RR: relative risk; CI: confidence interval; FEV1: forced expiratory volume in 1 s.

Follow-up results

Follow-up data were complete in all patients. Overall, 298 patients were discharged. The mean follow-up time was 3.9 years, ranging from 1 month to 10.4 years. Adjuvant postoperative chemotherapy was performed in 20 (6.3%) patients. Adjuvant chemoradiotherapy was performed in 3 (1%) patients. Radiation therapy only was performed in 13 (4.1%) patients who could not tolerate chemotherapy. Thirty-seven patients died due to causes not related to lung cancer (23%). The remaining 121 patients died due to systemic or local tumour recurrence (77%).

A total of 157 patients died during the follow-up period with an overall mortality of 52.7 weeks.

Disease recurrence was local in 80 patients and systemic in 41. Local recurrence included any recurrence within the ipsilateral lung, bronchial stump, the N_1–N_3 nodal disease and the ipsilateral pleural space. Systemic recurrence was defined as recurrence in the controlateral lung, liver, adrenal glands, bone, brain or other locations. At the end of the study, 141 patients were still alive, 118 of whom were free from cancer recurrence. The interval to recurrence was 5 ± 2.3 months (range 2–68 months). The overall survivals at 1, 3 and 5 years were 86, 59 and 38%, respectively (Fig. 1a). The disease-free survivals at 1, 3 and 5 years were 82, 60 and 47%, respectively (Fig. 1b). The long-term overall survival was negatively influenced by pneumonectomy (odds ratio [OR] 5.5, 95% confidence interval [CI] 1.95–15.5, $P < 0.006$), extended resection (OR 6.4, 95% CI 1.89–21.7, $P < 0.0001$; Fig. 2a and b), N_{1-2} subgroups (OR 2.8, 95% CI 1.05–7.27, $P < 0.001$) and pathological TNM stage (OR 4.8, 95% CI 1.28–18.2, $P < 0.001$; Fig. 3a and b). There was no statistically significant association between survival and preoperative comorbidities and histology ($P = 0.2$).

Table 4: Postoperative complications

Complications	No. of patients	Percentage
Overall morbidity	155	45.6
Postoperative AF	45	14
Atelectasis	47	14.7
Prolonged air leak	27	8.5
Prolonged ventilation	18	5.6
Bronchopleural fistula	3	0.9
Acute renal failure	6	2
Delirium	14	4.4
Haemothorax	7	2.2
Chylothorax	1	0.3
Empyema	1	0.3
Pneumonia	15	4.7
Bowel ischaemia	4	1.3
Postoperative AMI	17	5.3
ALI/ARDS	9	2.8
>1 Complication	58	37.4

AF: atrial fibrillation; AMI: acute myocardial infarction; ALI/ARDS: acute lung injury/acute respiratory distress syndrome.

DISCUSSION

The analyses of the operative risk and the identification of preoperative and operative risk factors for operative morbidity and mortality are the first issues that need to be addressed when surgery is considered in older patients. In the last few years, different authors demonstrated that lung resection in older patients may grant acceptable results in terms of in-hospital mortality and long-term prognosis. In the 1970s, the mortality ranged from 15 to 21%, in the 1990s, from 0 to 20%, whereas, after 2000, the reported in-hospital mortality ranged from 0 to 8.8% [7, 8, 12–16]. The difference in results can be due to a different and more accurate preoperative work-up including staging process, morbidity examination, and advances in anaesthesiological and surgical techniques. The 6.3% in-hospital mortality and 45.6% morbidity observed in our series are comparable with those reported in another study performed in the same period [8, 12, 13]. In 2007, Dominguez-Ventura *et al*. [8] reported an operative mortality of 6.3% in 379 octogenarians subjected to pulmonary resection for NSCLC. More recently, a French nationwide audit [9] showed a 30-day mortality of 6.5% in 622 patients >80 years. In 2011, Fanucchi *et al*. [13] reported a perioperative mortality rate of 2.4% in 82 patients >80 years. The major causes of death in our patients are related to cardiovascular complications according to other published series [6, 7, 12–15]. This high rate of cardiovascular events is justified by the high incidence of cardiovascular diseases even in asymptomatic older people. Usually, the preoperative cardiac evaluation is performed following the American College of Cardiology/American Heart Association guidelines or the guidelines from the European Society of Anaesthesiology for preoperative evaluation for non-cardiac surgery [16, 17]. The utility of a more complete and invasive preoperative cardiac evaluation to improve perioperative outcomes in such older patients is still unclear. Of seven patients who died of postoperative myocardial infarction, none had any previous history of ischaemic heart disease. Only one of these patients had been documented for a mild inferior hypoperfusion on myocardial scintigraphy performed because of a left bundle branch bloc, discovered on the preoperative EKG. Reportedly, acute respiratory failure is the second main cause of death, which is reflected by the high frequency of preoperative poor lung function in older patients [18–21]. In our study, according to other published series [8, 12], a low FEV1 was a risk factor for in-hospital mortality both at the univariate and multivariate

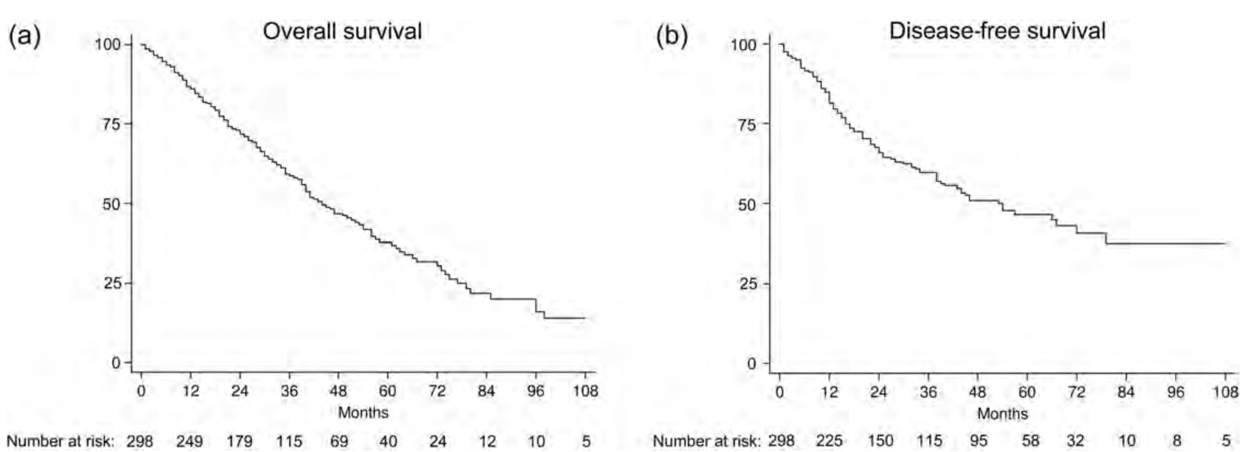
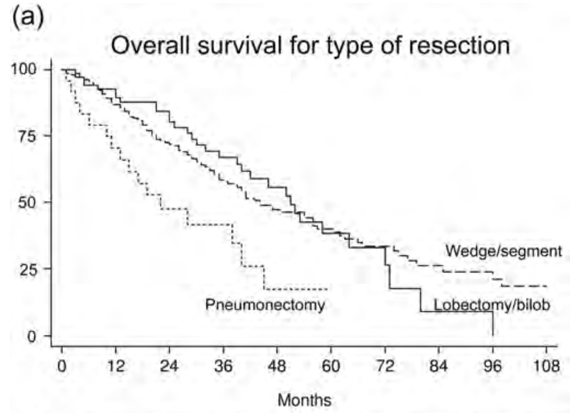
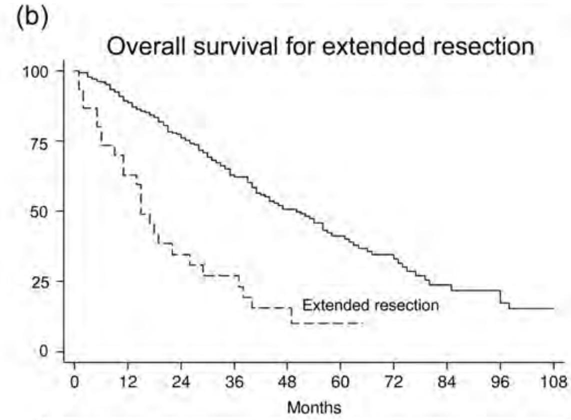


Figure 1: (**a**) Kaplan–Meier function of overall survival. (**b**) Kaplan–Meier function of disease-free survival.

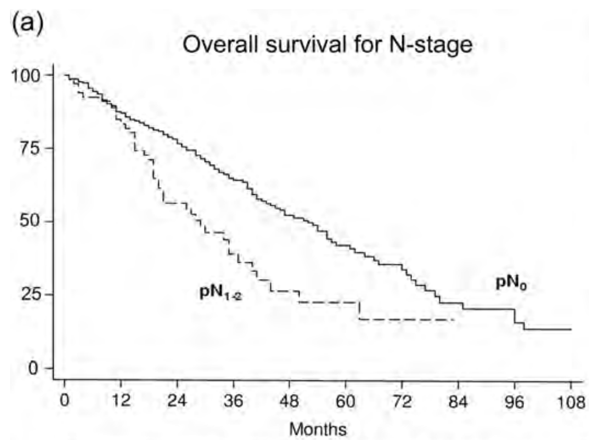


Type of resection	1-year OS (95%*IC*)	3-year OS (95%*IC*)	5-year OS (95%*IC*)	*P*-value
Wedge/segment	89(79–95)	67(52–78)	38(22–54)	
Lobectomy/bilob	87(81–91)	57(49–64)	40(32–48)	
Pneumonectomy	70(48–85)	42(21–61)	0	0.006

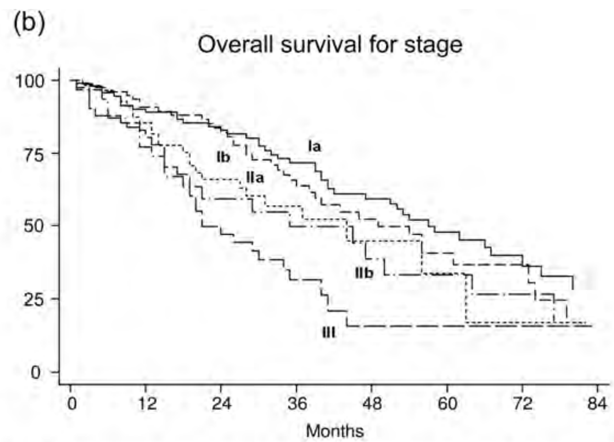


Extended resection	1-year OS (95%*IC*)	3-year OS (95%*IC*)	5-year OS (95%*IC*)	*P*-value
Yes	63(43–77)	27(12–44)	10(2–26)	
No	89(84–92)	62(55–68)	41(33–49)	<0.0001

Figure 2: (**a**) Kaplan–Meier overall survival stratified type of resection, (**b**) Kaplan–Meier overall survival stratified for extended resection.



N-factor	1-year OS (95%*IC*)	3-year OS (95%*IC*)	5-year OS (95%*IC*)	*P*-value
pN_0	87(82–91)	64(57–71)	42(34–50)	
$pN_{1\text{-}2}$	83(72–90)	62(26–52)	23(11–37)	0.001



Pathological stage	1-year OS (95%*IC*)	3-year OS (95%*IC*)	5-year OS (95%*IC*)	*P*-value
Ia	89(80–94)	72(60–80)	48(35–60)	
Ib	91(81–95)	64(51–74)	41(26–55)	
IIa	85(73–92)	57(40–70)	34(12–57)	
IIb	77(58–88)	50(30–67)	33(15–53)	
III	80(64–90)	31(17–47)	16(5–33)	0.001

Figure 3: (**a**) Kaplan–Meier overall survival stratified for N factors, (**b**) Kaplan–Meier overall survival stratified for pathological stage.

analyses ($P = 0.009$). This finding contrasts with the opinion of other authors [13, 14] who showed no difference in terms of operative mortality and morbidity when patients were stratified by poor lung function. It is possible that these different results reflect a selection bias and a lack of homogeneity in the evaluation and definition of 'poor lung function' [8, 12–14]. As expected given the intrinsic frailness and the low physiological reserve of older people, extended resection and advanced tumour stage are associated in our study and in the literature with poor operative and long-term results [12, 14, 16]. In particular, pneumonectomy emerges as prognosticator in the univariate and multivariate analyses ($P = 0.0001$). In the work of Fanucchi *et al.* [13], the extent of resection significantly influenced hospital mortality. In addition, Voltolini *et al.* [12] reported that extended resection was a predictor of major postoperative complications with a relative risk of 10.5. In their series, the mortality rate for pneumonectomy was 25%; a similar mortality after pneumonectomy was found in our experience also (23.3%). We now believe that pneumonectomy, in particular on the right side, should be avoided in older people and all efforts should be made to perform a parenchyma-sparing procedure. Zuin *et al.* [18] reported a 7.5% mortality in 40 older patients who underwent pneumonectomy for NSCLC. Also, in this study, right pneumonectomy was a strong risk predictor for in-hospital mortality. However, in the author's opinion, pneumonectomy appears to be a safe and justified operation even in elderly patients [18]. These encouraging results for older patients undergoing pneumonectomy reflect a really careful preoperative evaluation. Among mortality prognosticators on univariate analysis, the squamous histology, pathological stage and chronic renal failure were significantly related to in-hospital mortality. Other series reported different comorbidities as risk factors for operative results [7, 8, 12, 13, 19, 20]. Moreover, 70% of our patients had multiple comorbidities. Frequently, the operative risk is a function of not only a single comorbidity, but rather a set of them. Improvements in treatment decision-making can be expected by predictive models [19, 20]. Another issue to be addressed concerns the effects of surgery on long-term survival compared with the life expectancy. The survival data in our study revealed overall survivals at 1, 3 and 5 years of 86, 59 and 38%, respectively. The disease-free survivals at 1, 3 and 5 years were 82, 60 and 47%, respectively. These results are consistent with those reported in other series published recently, with an overall 5-year survival ranging from 27 to 56% [8, 12, 13, 15, 19, 22, 23]. This wide range in survival is likely due to some confounding factors: selection bias, small study population and incompleteness of follow-up. Moreover, the definition of older people is not uniformly accepted. Another confounding factor is the proportion of early and advanced pathological stages and the types of resection between published studies. Fanucchi *et al.* [13] reported a 5-year overall survival of 27% in a series with a significant prevalence of Stage III (34%). In their study, the pathological stage was statistically associated with poor survival. The 5-year overall survival reported by Okami *et al.* [15] was 55.7% with Stage pI representing 82% of the patient population. In our study, the pathological stage had a great influence on long-term results. Forty-seven patients were in pathological Stage III representing 14.7% of the study population. The overall 5-year survival of pathological Stage Ia was 48% compared with the 16% 5-year survival for pathological Stage III ($P < 0.001$). Pagni *et al.* [14] reported a 5-year survival for Stages pI and pIII of 57 and 0%, respectively. Dominguez-Ventura *et al.* [8] reported similar results with a 5-year survival for Stage pIa of 47.6% compared with 8.8% 5-year survival for Stage pIIIa. Voltolini *et al.* [12] reported a 5-year survival rate for Stage pI vs pIII of 60 and 14%, respectively. In our experience, lymph node involvement had a great influence on long-term survival. The 5-year overall survival of patients pN_0 was 42 vs 23% of patients with $pN_{1–2}$ ($P < 0.001$). As already reported by others [7, 16, 24], older patients with N_2 disease seem to have a poor prognosis compared with younger N_2 patients [12, 16]. In our series, pneumonectomy and extended resections represented additional risk factors for poor long-term survival. Indeed, the 5-year overall survival of patients undergoing pneumonectomy and extended resections was 0 and 10%, respectively. Different authors reported disappointing results in older patients subjected to pneumonectomy or other extended resections [7, 12, 14]. In our elderly patients, we had a very high in-hospital mortality and a 5-year survival almost close to 0%. Older patients with suboptimal performance status have been frequently treated with limited surgical resection such as wedge or typical segmentectomy without complete lymphadenectomy. In our experience, the in-hospital mortality and 5-year survival between sublobar and lobar resection as well the incidence of local recurrence were not significantly different. The present study has several limitations that must be taken into account during the analysis of the results. First, it is a retrospective study. Elderly patients who underwent surgery represent a category of selected patients, particularly in terms of preoperative morbidity and performance status. Analysing data collected over a period of 10 years shows that the selection criteria changed on the basis of advancements in the diagnosis, surgical techniques, anaesthetic management and postoperative care. In this study, all patients were re-staged using the last TNM system, and this may have had implications for treatment protocols used in these patients.

In conclusion, older age is not a contraindication to lung surgery for NSCLC. The operative mortality improved over the years and, nowadays, we can consider surgery a safe and justifiable option for elderly patients. Careful preoperative work-up and selection are mandatory to gain satisfactory results. Particular attention should be paid to the evaluation and quantification of the patient's cardiovascular and respiratory comorbidities. Good long-term results were achieved in elderly patients with early stage who underwent lobar or sublobar lung resection. The role of surgery or other alternative therapies in patients with advanced stages, extensive nodal involvement and/or requiring extensive surgical resection for curative intent, is still unclear and further studies are certainly needed.

Conflict of interest: none declared.

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