

# Prognostic Factors for the Survival of Surgically Treated Patients for Non-Small Cell Lung Cancer

Oswaldo J.C.B. Fernandes, Stig-Olof Almgren, Lars Thaning, Derek Filbey, Martin Helsing, Mats Karlsson, Anders Magnusson and Domingos Souza

From the Departments of Cardiothoracic Surgery (O.J.C.B. Fernandes, S.-O. Almgren, D. Souza), Pulmonary Medicine (L. Thaning), Transfusion Medicine (D. Filbey), Oncology (M. Helsing), Pathology (M. Karlsson) and the Centre for Clinical Research (A. Magnusson), University Hospital, Örebro, Sweden

Correspondence to: Oswaldo J. C. B. Fernandes, Department of Cardiothoracic Surgery, Örebro University Hospital, SE-701 85 Örebro, Sweden. Tel: +46 19 6025 222. Fax: +46 19 6113 943. E-mail: oswaldo.fernandes@orebroll.se

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The survival and outcome rates of 284 patients who underwent surgical treatment for non-small cell lung cancer were assessed retrospectively. Resectability rate was 94.1%, hospital mortality 3.9% (n = 11) and the mortality rates in patients who underwent pneumonectomy or lobectomy were 8.9% and 0.6%, respectively. The overall 5-year survival was 43.6%. Female gender, earlier stages of disease and a complete resection were strongly predictive for a long-term survival. Women in stage IA disease had a 5-year survival rate of 92.7%. The 5-year survival rate for patients in stages IIIA and N2 disease who underwent a complete resection was 21.9%, and 9% for those who did not undergo a complete resection. It is concluded that the best surgical results were observed in women who were operated on at an early stage of disease. A complete resection also contributed to a better outcome, even for patients in stage IIIA and N2 disease.

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Carcinoma of the lung has become a major health problem since it is the most common cause of death from cancer in western countries (1). In Sweden about 2600 cases of lung cancer are diagnosed yearly, and only about 20% of them benefit from surgical treatment (2). There is general agreement that surgical resection of the tumour has a central role in long-term survival (3). Multiple factors have been implicated in the outcome, and these can be categorized as clinical-, tumour- and treatment related factors (4). Lung carcinoma is therefore considered a complex disease that constitutes a challenge to both clinicians and surgeons regarding the best form of treatment for each individual.

The objective of this study was to evaluate retrospectively the results of our pulmonary resections for non-small cell lung cancer (NSCLC) regarding the influence of different factors on postoperative long-term survival.

## MATERIAL AND METHODS

### *Patients and preoperative evaluation*

The clinical, surgical and pathological records of 284 patients who underwent surgical treatment for NSCLC at

Örebro University Hospital, Sweden, between 1 January 1990 and 31 December 1995 were analysed.

An evaluation of pulmonary- and cardiac function was done routinely. Fourteen patients had a history of heart disease, such as previous myocardial infarctions, angina pectoris or myocardial ischaemia at ECG-ergometry. Two patients had chronic bronchitis with reduced respiratory function. Bronchoscopy was performed in 260 patients. CT scans were carried out in 283 patients in order to evaluate both the localization of the tumour and the involvement of mediastinal nodes. Mediastinoscopy was performed in only 34 patients.

One of 6 patients in clinical stage IIB received radiotherapy preoperatively. One of 6 patients in clinical stage IIIB received both radio and chemotherapy, and another patient received laser and radiotherapy. Two patients who underwent a craniotomy for solitary cerebral metastasis were found to have primary lung tumours.

### *Surgery, pathological evaluation and oncological treatment*

At thoracotomy the tumour was extirpated either by lobectomy, pneumonectomy or wedge-excision, according to the size, location of the tumour and the patient's lung

and cardiac function. Mechanical stapling of the bronchi was used in all cases. Neither radical mediastinal nodal dissection nor systematic sampling of lymph nodes was performed routinely. The extent of the lymph node resection was decided during surgery based only upon palpation or appearance of the nodes. The whole surgically excised tumour was examined histopathologically, and was evaluated for completeness of the resection. A resection was considered complete if the entire tumour was resected macroscopically, and the surgical margins were free of disease microscopically. The disease was staged by the international TNM criteria for cancer staging established by the American Joint Committee on Cancer (AJCC), revised in 1997 (5).

Thirty-nine patients received further therapy postoperatively with radiation, chemotherapy or combined treatment. The oncological treatment was based on clinical data, completeness of the resection and/or the presence of N2 disease.

The follow-up was obtained from hospital records, the health authorities, or by telephone contact. The mean follow-up time was 36.7 months (range 1–104 months).

#### Statistical methods

Postoperative mortality included the patients who died in the first 30 days after the surgical intervention, even if they died later during the same period of hospitalization. All these patients were also included in the survival analysis. The survival rates were calculated using the Kaplan–Meier method. An observation was complete at the last follow-up if the patient died of lung cancer or postoperative complications. The differences in survival rates were calculated using the log-rank test. We performed a Cox's proportional hazard regression analysis (6) to identify prognostic factors that influence long-term survival and the relationship between them in resected patients. We investigated the effects of gender, age ( $> 70$ ,  $\leq 70$  years), type of pulmonary resection (lobectomy/lesser resections, pneumonectomy and bilobectomy), histopathological type (squamous-, adeno- and large cell carcinoma), completeness of the resection (complete and incomplete) and stage (IA, IB, IIA + IIB and IIIA). The prognostic factors were studied in a univariate analysis, and only those factors with a p-value  $< 0.20$  were included in the multivariate model. STATA (Stata Statistical Software: Release 7.0. College Station, TX: Stata Corporation) was used in all statistical analyses. Results were considered statistically significant at a p-value  $< 0.05$ .

## RESULTS

The study included 183 men and 101 women, mean age 63.8 years (range 36–82). The histopathological types of tumour are listed in Table 1.

**Table 1**

*Distribution of lung cancer related to histopathology and gender*

Histopathological type	Male	Female	Total
Squamous carcinoma	100 (54.6%)	24 (23.8%)	124
Adenocarcinoma	68 (37.2%)	69 (68.3%)	137
Large cell carcinoma	12 (6.6%)	6 (5.9%)	18
Mixed types	1 (0.5%)	2 (2%)	3
Low differentiated carcinoma	2 (1.1%)	0 (0%)	2
Total	183	101	284

The tumour was located in the upper lobe in 139 patients (48.9%), lower lobe in 70 (24.7%), right middle lobe in 8 (2.8%) and more than one lobe in 67 patients (23.6%).

The resectability rate was 94.1% (267/284). Lobectomy was performed in 163 (57.4%) patients, pneumonectomy in 79 (27.8%), bilobectomy in 13 (4.6%), lobectomy associated with wedge resection in 7 patients (2.5%) and wedge resection alone in 5 (1.8%). In 8 patients the tumour had invaded the chest wall. In such cases the pleura parietalis adjacent to the tumour was resected in 5 patients, and in 1 patient the surrounding chest-wall area was resected without reconstruction. A complete resection was not achieved in 45 patients (15.8%). In 17 (5.9%) of these patients no resection was undertaken because the tumour was considered unresectable at the thoracotomy.

Thirty-three of 34 mediastinoscopies were negative. Nevertheless, N2 disease was found at thoracotomy in 11 patients in this group.

**Table 2**

*Postoperative pathological classification of 284 patients according to TNM pathological stage*

TNM	No. patients	Stage	Total
T1N0M0	87	IA	87 (30.6%)
T2N0M0	87	IB	87 (30.6%)
T1N1M0	4	IIA	4 (1.4%)
T2N1M0	38	IIB	45 (15.9%)
T3N0M0	7		
T3N1M0	2	IIIA	34 (12%)
T1N2M0	7		
T2N2M0	21		
T3N2M0	4		
T4N0M0	12	IIIB	17 (6%)
T4N1M0	1		
T4N2M0	4		
T1N0M1	3	IV	10 (3.5%)
T2N0M1	2		
T3N0M1	1		
T2N2M1	3		
T3N2M1	1		
Total	284		

The final pathological classification for each patient is presented in Table 2. In 7 of 27 patients with stage IIIB and IV disease, the right classification was made preoperatively, and in the remaining 20 the classification was determined peroperatively.

The rate of hospital mortality was 23% (3/13) for patients who underwent bilobectomy, 8.9% (7/79) for patients who underwent pneumonectomy, and only 0.6% (1/163) for patients who underwent lobectomy. Accordingly, the hospital mortality was 3.9% (11/284). The causes of death were myocardial infarction in 4 patients, heart failure in 1 patient, respiratory failure in 1 patient, pneumonia followed by respiratory failure in 2 patients and pneumonia followed by pulmonary embolism in 1 patient. None of these patients had any history of previous heart disease. Bronchopleural fistula was observed in 1.2% (2/163) of the patients who underwent a lobectomy, and in 7.6% (6/79) of the patients who underwent a pneumonectomy; for 2 of these patients this complication was fatal.

The survival rates at 1, 3 and 5 years were 73.8%, 51.2% and 43.6%, respectively. The survival curves and 5-year survival rate according to the stages are shown in the Fig. 1.

The 5-year survival rate for 239 patients who underwent a complete resection was 51.3%, and for the 45 patients who had an incomplete resection, the rate was 3.3%.

The 5-year survival rate for 21 of 32 patients with N2 disease in stage IIIA who underwent a complete resection was 21.9%, whereas for the remaining 11 patients who underwent an incomplete resection the rate was 9%. None of the patients in stage IIIB and IV survived 3 years.

Five-year survival for women and men was 64.7% and 32.1%, respectively ( $p < 0.001$ ). The survival rate in each stage and the difference by gender are shown in Table 3. The longest survival rate was found in female patients who were in stage IA disease. Women also had a better long-term survival in all other stages.

In a univariate analysis it was found that all the factors studied influenced the outcome significantly, with the exception of age ( $p = 0.48$ ) and histopathological type

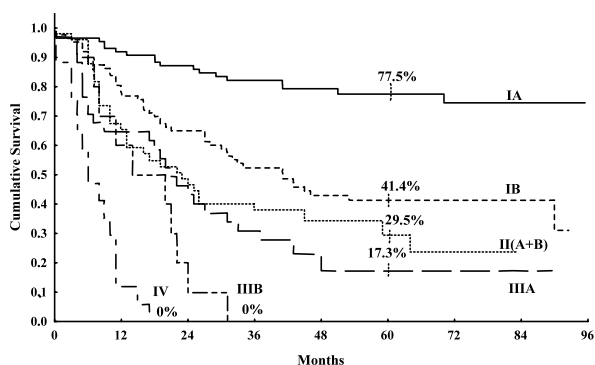


Fig. 1. Survival curves and 5-year survival rates according to different stages for 284 patients who underwent thoracotomy for non-small cell lung cancer.

Table 3

Survival rates in the 'surgical stages' according to gender

Stage	Male/ female (n)	5-year survival rate		p-value (log-rank)
		Male	Female	
IA	42/45	61.5%	92.7%	< 0.01
IB	69/18	36.5%	60.6%	= 0.12
II(A+B)	34/15	16.8%	60%	< 0.05
IIIA	19/15	8.6%	26.7%	= 0.09

Table 4

Relative hazard rates and 95% confidence interval for different factors (Cox Model)

	Multivariate analysis	p-value
Gender		
Female	1.0 (ref.)	< 0.01
Male	2.1 (1.3–3.3)	
Type of Resection		
Lobectomy/lesser Resection	1.0 (ref.)	0.40
Pneumonectomy	1.7 (0.8–3.6)	
Bilobectomy	1.2 (0.8–1.7)	
Complete resection		
Yes	1.0 (ref.)	< 0.01
No	2.8 (1.5–5.0)	
Stage		< 0.01
IA	1.0 (ref.)	
IB	2.6 (1.5–4.6)	
II (A+B)	3.4 (1.8–6.5)	
IIIA	4.5 (2.3–8.8)	

Abbreviation: ref. = reference group.

( $p = 0.60$ ). A multivariate analysis showed that the type of resection had no significant effect on long-term survival. However, female gender, earlier stages and a complete resection were significant independent factors for long-term survival (Table 4).

DISCUSSION

Our study showed that female gender, earlier stage of disease and a complete resection, even for stages IIIA and N2 disease, were important independent factors for a better long-term survival after surgical treatment for NSCLC. A very high 5-year survival was achieved in women who were in stage IA.

The prognosis for patients subjected to surgical treatment for NSCLC is mainly determined by the stage of the disease. We have achieved a 5-year survival rate of 77.5% for patients in stage I, which is in agreement with other studies (7, 8).

However, unlike other studies (9, 10), we found low survival rates for patients in stage IB and stage II. We believe that some of these patients had N2 disease and were wrongly down-staged, since neither sampling nor radical mediastinal lymphadenectomy was performed.

The surgical treatment for patients in stage IIIA and N2 disease is still controversial due to poor surgical results. In selected cases a surgical resection was found to be associated with a satisfactory rate of long-term survival (11). We performed a complete resection in 65.6% of patients in stage IIIA and N2 disease, and the 5-year survival rate for these patients was 21.9%.

A higher rate of complete resection in patients with stage IIIA and N2 disease has been demonstrated when mediastinoscopy is carried out in addition to screening (12). Moreover, it was reported that patients in stage IIIA and N2 disease that had a negative mediastinoscopy showed a better long-term survival than those with a positive one (13). Our 5-year survival rate was concordant with these studies. The high rate of false negatives and the fact that we performed mediastinoscopy in only a few patients might have contributed to the incomplete resection in many of our patients in this group. Nowadays we perform mediastinoscopy routinely in almost all patients who undergo surgical treatment for NSCLC.

Some studies of selected subgroups of patients in stage IIIB and IV have demonstrated good surgical results (14, 15). However, our results for patients in these stages were poor, and none of them survived 3 years.

In agreement with another study (16) we could demonstrate that extensive lung resections did not influence the late outcome, but in our study extensive resections influenced the early outcome owing to complications associated with pneumonectomy and bilobectomy.

The reasons for a better long-term survival in women are still unclear. One reason seems to be associated with the reproductive hormones. It has been demonstrated that oestrogen receptors are present in NSCLC tissue in 96.8% of patients who were surgically treated, whereas no receptors were found in normal lung cells (17). Another report has shown a statistically significant correlation between oestrogen receptor-related protein p29 and a longer survival for women, which was most pronounced in the earlier stages (18). These results are interesting, and they open a new area of investigation in this field, which might help to elucidate the influence of gender on lung carcinogenesis in the future.

In conclusion, our study showed that surgical treatment for patients with NSCLC in stage IA was associated with a high long-term survival, especially for women. A complete resection was also associated with good results, even in patients with stage IIIA and N2 disease. We observed that if we had carried out more mediastinoscopic examinations, we would certainly have performed a higher rate of complete resections, as well as preventing unnecessary thoracotomies.

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#### REFERENCES

- Black R, Bray F, Ferlay J, Parkin D. Cancer incidence and mortality in the European Union: cancer registry data and estimates of national incidence for 1990. *Eur J Cancer* 1997; 33: 1075–107.
- National Health Program for Lung Cancer—2001. Regional Oncological Centre at Uppsala/Örebro Region.
- Overholt RH, Neptune WB, Ashraf MM. Primary cancer of the lung. A 42-year experience. *Ann Thorac Surg* 1975; 20: 511–9.
- Jazieh AR, Hussain M, Howington JA, et al. Prognostic factors in patients with surgically resected stages I and II non-small cell lung cancer. *Ann Thorac Surg* 2000; 70: 1168–71.
- Mountain CF. Revisions in the international system for staging lung cancer. *Chest* 1997; 111: 1710–7.
- Cox DR. Regression model and life tables. *JR Stat Soc* 1972; B34: 187–220.
- Nesbitt JC, Putnam JB Jr, Walsh GL, Roth JA, Mountain CF. Survival in early-stage non-small cell lung cancer. *Ann Thorac Surg* 1995; 60: 466–72.
- Williams DE, Pairolero PC, Davis CS, et al. Survival of patients surgically treated for stage I lung cancer. *J Thorac Cardiovasc Surg* 1981; 82: 70–6.
- Martini N, Bains MS, Burt ME, et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. *J Thorac Cardiovasc Surg* 1995; 109: 120–9.
- Martini N, Burt ME, Bains MS, McCormack PM, Rusch VW, Ginsberg RJ. Survival after resection of stage II non-small cell lung cancer. *Ann Thorac Surg* 1992; 54: 460–5.
- Mountain CF. Surgery for stage IIIa-N2 non-small cell lung cancer. *Cancer* 1994; 73: 2589–98.
- Goldstraw P, Mannam GC, Kaplan DK, Michail P. Surgical management of non-small cancer with ipsilateral mediastinal node metastasis (N2 disease). *J Thorac Cardiovasc Surg* 1994; 107: 19–28.
- Pearson FG, DeLarue NC, Ilves R, Todd TRJ, Cooper JD. Significance of positive superior mediastinal nodes identified at mediastinoscopy in patients with resectable cancer of the lung. *J Thorac Cardiovasc Surg* 1982; 83: 1–11.
- Rendina EA, Venuta F, De Giacomo T, et al. Induction chemotherapy for T4 centrally located non-small cell lung cancer. *J Thorac Cardiovasc Surg* 1999; 117: 225–33.
- Billing PS, Miller DL, Allen MS, Deschamps C, Trastek VF, Pairolero PC. Surgical treatment of primary lung cancer with synchronous brain metastases. *J Thorac Cardiovasc Surg* 2001; 122: 548–53.
- Fang D, Zhang D, Huang G, Zhang R, Wang L, Zhang D. Results of surgical resection of patients with primary lung cancer: a retrospective analysis of 1 905 cases. *Ann Thorac Surg* 2001; 72: 1155–9.
- Canver CC, Memoli VA, Vanderveer PL, Dingivan CA, Mentzer RM Jr. Sex hormone receptors in non-small cell lung cancer beings. *J Thorac Cardiovasc Surg* 1994; 108: 153–7.
- Vargas SO, Leslie KO, Vacek PM, Socinski MA, Weaver DL. Estrogen-receptor-related protein p29 in primary non-small cell lung carcinoma: pathologic and prognostic correlations. *Cancer* 1998; 82: 1495–500.