

Disease recurrence after resection for stage I lung cancer¹

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Abstract

Objective: To assess the incidence of local recurrence and distant metastases after complete resection for stage I lung cancer in order to predict the predominant prognostic factors. **Method:** We retrospectively reviewed 123 patients with stage I lung cancer who underwent curative resection over a 2-year period between January 1987 and December 1988. There were 83 male and 40 female patients with a mean age of 64.8 ± 12 years (range between 39 and 82 years). Multivariate analysis of prognostic factors for long term survival was undertaken. **Results:** T1N0 lesions were found in 34 patients and T2N0 in 89. The histological diagnosis was Squamous carcinoma in 75, Adenocarcinoma in 38, large cell carcinoma in 6 and small cell carcinoma in 4 patients. Pneumonectomy was performed in 27 patients (5 T1 and 22 T2) while 96 required lobectomy (29 T1 and 67 T2). At 5 years 50 patients died. This was due to local recurrence in 12, distant metastasis in 24, second primary in 1, unrelated disease in 3, while the cause was unknown in 10 patients. At 5 years, 10 patients were alive with evidence of recurrence. The mean interval for local recurrence was 19.8 months and for distant metastasis was 18 months. The overall 5 year survival was $67\% \pm 4$ for T1 and $56\% \pm 5$ for T2 lesions (NS). The rate of recurrence was significantly less for T1 lesions ($P = 0.02$). Survival was significantly less for patients requiring pneumonectomy rather than lobectomy ($P = 0.01$) whether for T1 or T2. **Conclusion:** In stage I lung cancer T2 lesions requiring pneumonectomy for complete resection had a worse prognosis and higher incidence of local recurrence. © 1997 Elsevier Science B.V.

Keywords: Lung cancer; Recurrence; Metastasis; Surgery

1. Introduction

Surgical resection for patients with stage I lung cancer carries the best prognosis [1]. Despite attempts at curative resection the 5 year survival ranges between 75 and 60% [12]. Local recurrence and distant metastasis remain the commonest cause of death in those patients [8]. Previous reports did not agree on specific prognostic factors in this group of patients [3,5–7]. The purpose of our study is to determine the incidence and pattern of local recurrence and distant metastasis after complete resection in patients with stage I lung cancer

and to identify the predominant prognostic factors influencing survival in those patients.

2. Patients and methods

Over a period of 2 years, between January 1987 and December 1988, curative resection was performed for 123 patients with stage I lung cancer. These patients represented 61.5% of all patients operated upon for lung cancer during that period [2]. The overall operative mortality was 2.8% for lobectomies and 5.3% for pneumonectomies. All patients were followed up for a minimum of 5 years or until their death with a mean follow up period of 53.9 ± 27 months (range between 4 and 90 months). There were 83 male and 40 female patients with a mean age of 64.8 years (range between

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Table 1
Univariate analysis of factors influencing survival in 123 patients with complete resection for stage I lung cancer

Prognostic factor	3-Year survival (%)	5-Year survival (%)	X2	P value
Tumour size				
T1 (n = 34)	80.2	67.6	1.537	0.19
T2 (n = 89)	62.9	56.2	—	—
Histological type				
Sq (n = 76)	67	63	0.612	0.89
Adeno (n = 37)	64	54.5	—	—
Others (n = 10)	50	50	—	—
Sex				
Male (n = 83)	66.3	59	0.247	0.62
Female (n = 48)	65	60	—	—
Age				
< 60 y (n = 26)	64.3	57.5	0.342	0.52
> 60 y (n = 97)	67.2	58.9	0.653	0.47
Side				
Right	72	62.2	0.453	0.50
Left	68	56.2	—	—
Operation				
Lobectomy (n = 96)	71.9	63.5	5.185	0.02*
Pneumonectomy (n = 27)	48.1	44.4	—	—
Symptom				
Asymptomatic (22)	58	58	0.020	0.89
Symptomatic (101)	67.5	59	—	—

Sq, Squamous cell carcinoma; Adeno, Adenocarcinoma.

* $P < 0.05$ considered statistically significant.

39 and 82 years). The histological diagnosis was Squamous cell carcinoma in 75, Adenocarcinoma in 38, Large cell carcinoma in 6 and Small cell carcinoma in 4 patients. All patients were classified to be in stage I according to the new international classification [11], 34 with T1 N0 lesion and 89 with T2 N0 lesion.

Cough was the predominant presenting symptom, being present in 64% of the patients followed by hemoptysis in 49%. Asymptomatic patients accounted for 19%.

Pre-operatively, patients were assessed by computerised thoracic scan with or without mediastinal lymph node biopsy. The preoperative criteria not to perform mediastinal lymphnode biopsy included peripheral tumours with no visible endobronchial lesion and normal size mediastinal nodes (less than 10 mm) as detected by computerised mediastinal scan. Posterolateral thoracotomy was the standard surgical access and mediastinal lymph node sampling was performed for all patients for accurate staging. Curative resection required lobectomy in 96 patients, 29 for T1 lesions and 67 for T2 lesions. Pneumonectomy was found to be necessary for complete resection in 27 patients, 5 with T1 and 22 with T2 lesions. Patients were followed up by periodic physical and radiological examinations for a minimum period of 5 years or until their death. Local recurrence was identified as a tumour of the same cell type occurring at

the same anatomical site including disease of the ipsilateral mediastinum (regional recurrence) after any disease-free period [10]. Distant metastasis was defined as contralateral thoracic or any extrathoracic presentation of metastatic disease [10]. A second primary was identified as tumour of different cell type or anatomical site occurring after a period exceeding 2 years from the first operation [1]. Adjuvant therapy was only used after diagnosis of recurrence.

The overall survival and recurrence-free interval rates were calculated using the Kaplan–Meier method. The cause of death was identified in 80% of the cases (40 out of 50 cases). Difference in survival and recurrence rate were calculated using the log-rank test and the difference in frequency using χ^2 test. A P value ≤ 0.05 was considered significant. Cox proportional hazards model was applied for multivariate analysis.

3. Results

The 3- and 5-year survival was $72.5\% \pm 4$ and $60\% \pm 5$, respectively. For the T1 and T2 lesions the 5-year survival was $67.6\% \pm 4$ and $56.2\% \pm 5$, respectively. Multiple factors were tested against survival and recurrence which included age, sex, cell type, tumour size (T factor), side, symptomatic presentation, and type of

Table 2
Distribution of prognostic factors for recurrence-free survival

Factors	Observed recurrence	Recurrence risk	Relative rate	X2	P value
Size					
T1	11	14.99	0.734	2.657	0.02*
T2	39	35.01	1.114	—	—
Type					
Squamous	26	16.5	0.641	3.12	0.04*
Adenocarcinoma	17	42.6	1.362	—	—
Side					
Right	25	27.36	0.914	0.576	0.43
Left	24	22.65	1.10	—	—
Operation					
Lobectomy	35	40.74	0.859	6.258	0.01*
Pneumonectomy	15	9.26	1.619	—	—
Sex					
Male	34	33.24	1.023	0.273	0.82
Female	16	16.758	0.954	—	—
Asymptomatic	5	4.708	1.061	0.053	0.90
Symptomatic	45	45.29	0.99	—	—

* $P < 0.05$ considered a predominant prognostic factor.

resection. The log-rank test was used to compare the survival curves, and statistical evaluation of the related factors were calculated using the chi-square test (Table 1). Only type of resection was considered to be a significant prognostic factor in univariate analysis ($P = 0.02$). On multivariate regression analysis pneumonectomy was also a predominant prognostic factor ($P = 0.03$) (Table 3).

At 5 years 50 patients were dead. The cause of death was identified to be local recurrence in 12 (24%), distant metastasis in 24 (48%), cardiac causes in 3, and second primary in 1 patient. The cause of death was not confirmed in 10 patients (20%). There were additional 10 patients (8.1%) who were alive with evidence of the disease at 5 years postoperatively. Those patients were receiving adjuvant therapy for local recurrence ($n = 6$) and distant metastasis ($n = 4$) raising the incidence of these occurrences to 15 and 23%, respectively. The mean interval for local recurrence was 19.8 ± 3 months (range between 6 and 72 months) and for distant metastasis 18.2 ± 6 months (range between 2 and 60 months). The commonest site for distant metastasis was the brain (40%) followed by liver and contralateral mediastinum (16% each). Positive evidence of bone metastasis at the time of presentation was noted in 11% of these patients. Univariate analysis showed that T2 ($P = 0.02$), Adenocarcinoma ($P = 0.04$) and pneumonectomy ($P = 0.01$) are significant adverse prognostic factors (Table 2). Type of resection was the only independent factor for poor prognosis and higher rate of recurrence using the Cox proportional hazards regression model (Table 3).

4. Discussion

Surgical resection with curative intent is always attempted when operating for stage I lung cancer [2]. That usually include lobectomy or pneumonectomy with mediastinal lymph node clearance. The use of postoperative adjuvant therapy is usually limited to patients with residual disease or if they presented with recurrence [4]. As the long term survival in patients with lung cancer correlate with the pathological stage, better results are expected in patients with stage I [12]. The reported 5-year survival ranges between 50 and 75% and the cause of death is not limited to distant metastasis but a high incidence of local recurrence has also been reported [9]. In this study we analysed the patients with stage I lung cancer in whom complete resection was performed to identify the pattern and the prognostic factors determining survival and recurrence. The overall survival in stage I disease was 60% which is similar to the previously reported rates [11,12]. Although T1 lesions had a more favourable prognosis than T2 lesions that was not statistically significant. These findings are similar to those observed by Ichinose [6]. Similarly patients with squamous carcinoma had

Table 3
Independent factors influencing survival

Factors	P value	Risk ratio
Pneumonectomy	0.03*	1.62
Adenocarcinoma	0.12	1.17
T2	0.08	1.46

* $P < 0.05$ considered a predominant prognostic factor.

marginally better 5-year survival than other cell types but with no significance. Side of resection, age, sex, or symptoms did not influence survival. Despite the presence of 22 asymptomatic patients, they did not have better long term results. Patients who required lobectomy for curative resection showed significantly better survival when compared to patients in whom curative resection necessitated pneumonectomy. Type of resection was a predominant prognostic factor in our study. Other studies reported variable other prognostic factors but that was not consistent [3,6,7]. These factors included the grade of differentiation, vascular invasion, and symptomatic patients. With the introduction of immunohistochemistry assay different types of oncoproteins were reported to influence survival, especially p53—the tumour suppressor gene [5].

Martini (1995) reported an overall incidence of recurrence of 27% (Local or regional 7% and systemic 20%) in resected stage I lung cancer [9]. This incidence was as high as 50% in patients who had complete resection in form of segmentectomy or wedge resection [14].

In the present series the overall incidence of recurrence was 38%. The incidence of distant metastasis was similar to other reported incidence being 23% [14]. On the other hand we have observed a higher incidence of local or regional recurrence (15%). That could be explained that lymph node dissection was carried out as a tool for better staging rather than being performed to improve survival. This may have resulted in understaging some of the N2 disease in our patients. Cases in which segmental or wedge excision was performed to treat T1 lung cancers were not included in our study because they lack accurate staging and we do not consider the procedure a curative or complete [15]. There was no difference in the time interval between local or distant metastasis, both had a mean period of less than 2 years. With respect to pattern of distant metastasis brain was the commonest site followed by liver and lymphnodes which is similar to the pattern reported before in lung cancer patients [13]. On univariate analysis more factors influenced the incidence of recurrence including T factor, cell type, and type of resection. On multivariate analysis only T factor and type of resection were found to be independent prognostic factors. In all, 1 patient developed a second primary lung cancer indicating continuous exposure to risk factor rather than incomplete resection as stated by the Lung Cancer Study Group [14].

We conclude that despite complete resection for patients with early stage lung disease, survival rates are still in the range of 50–60%. Those patients are at high risk of developing local recurrence and distant metastasis. That emphasise the need for careful long-term follow up in order to detect and manage early recurrence by the appropriate adjuvant treatment or to detect a second malignancy. Lower survival rate and

higher incidence of recurrence are associated with patients with T2 N0 lesions in whom complete resection necessitates pneumonectomy. The needs for pneumonectomy in those patients are a tumour at the hilum or a tumour crossing the major fissure. Routine dissection of mediastinal lymph node provides better staging and may improve survival and reduce the incidence of recurrence, but further controlled studies are needed to further evaluate its importance.

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Appendix A. Conference discussion

Dr Granone (Rome, Italy): Are you sure that with mediastinal lymph node sampling you can achieve correct staging of your situation? Don't you think that, as you write in your conclusions, a complete radical lymphadenectomy of the mediastinum could decrease the number of your first stage, but increase the survival of the same number?

Mr Al-Kattan: Yes, I totally agree with you. These studies were on patients who were performed in 1987 and 1988, just to have actual complete 5-year survival in every patient rather than actuarial survival, and we can analyze the causes of death in each. But of course, our routine now is to have an extensive lymph node sampling, or extensive lymphadenectomy, at all stages to improve staging in this group of patients. We noted people who have been looking to N3 in early stage, they note 2–3% of T1 lesions to be associated with N3

despite the negative presence of cancer in the N1 and N2 group of patients. Indeed, complete lymphadenectomy gives better staging.

Dr Chervenikov (Sofia, Bulgaria): Firstly, I would like to congratulate you for the sophisticated analysis of such significant experience. Secondly, I would like to ask you a question. Have you, in your practice, ever had bronchoplasty procedures, wedge and sleeve resections of the bronchi, with T1 and T2 tumors? In our practice for the last several years we have had 5 cases local recurrence of the tumor after bronchioplasty procedures in more than 5, 6, 7 or 8 years after the operation. Of course, we are talking about no cases. We have also performed lymphadenectomy and cleaning of all visible lymph nodes despite the fact that only inflammatory changes were confirmed. Have you had an experience with local recurrence after the bronchioplastic anastomoses and lymph node dissection?

Mr Al-Kattan: Some of the cases actually were performed by sleeve resection and some, because of the respiratory status of the patient, required segmental or wedge resection. But I haven't included those in our study because it's not yet proved that this is actually a complete curative. So that will influence the incidence of local recurrence just due to the surgical procedure. I've only included cases in which lobectomy or pneumectomy was performed and excluded wedge and sleeve resections.