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Factors affecting long term survival following resection for lung cancer

K Al-Kattan, E Sepsas, E R Townsend, S W Fountain

Abstract

***Background* – Survival following pulmonary resection for primary lung cancer is considered to be principally dependent on the clinical stage of the disease. A study was undertaken to verify this and to identify other contributing factors.**

***Methods* – The case records of all patients who underwent surgery for lung cancer over a two year period between January 1987 and December 1988 were reviewed retrospectively.**

***Results* – One hundred and forty seven lobectomies and 60 pneumonectomies were performed with 2.8% and 5.3% operative mortality, respectively. Squamous carcinoma was the commonest pathology (60%) followed by adenocarcinoma (30%). The overall five year survival was 45.5% (95% CI 44.1% to 57.9%). There were 123 patients with stage I disease, 40 with stage II, and 37 in stage IIIa with five year survival of 59.4% (95% CI 50.8% to 68%), 30% (95% CI 15.9% to 44.1%), and 16.2% (95% CI 3.5% to 31%), respectively. There were no differences in survival with respect to sex, extent of resection, or cell type. In patients with stage II disease the five year survival of those with T1 lesions (50%, 95% CI 37.3% to 62.9%) was better than those with T2 (28.1%, 95% CI 16.9% to 39.3%). Of eight patients over the age of 70 with stage IIIa disease none survived more than 24 months.**

***Conclusions* – Stage at operation is the most accurate predictor of long term survival in early lung cancer and surgery remains an effective treatment, particularly in stage I and II disease. Further study is needed to assess the prognostic value of subdividing stage II disease into T1 and T2 lesions. Major resection for locally advanced disease in older patients may be relatively ineffective.**

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Keywords: lung cancer, survival, staging.

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The new international TNM staging system for lung cancer[1] has shown that good correlation exists between tumour stage at diagnosis and the chances of long term survival. Studies from North America and Japan[2] have confirmed that patients with tumours confined within the lung and without lymph node spread (stage I) have a significantly better prognosis than those with invasive tumours and mediastinal lymph node involvement (stage IIIa).

In this study we have reviewed retrospectively all patients who underwent pulmonary resection for primary lung cancer at our institution over a two year period at least five years ago to confirm the above relationship and to identify any other factors important in predicting actual long term survival.

Methods

Two hundred and seven patients with primary lung cancer underwent pulmonary resection between January 1987 and December 1988. There were 143 lobectomies and 57 pneumonectomies with an operative mortality of 2.8% and 5.3%, respectively. Complete follow up was available for all 200 patients who survived surgery, of whom 142 were men, and the mean age was 64 years (range 39–83). Squamous cell carcinoma was the commonest cell type being present in 120 patients (60%) followed by adenocarcinoma in 61 (30%).

There were 123 patients (83 men) with stage I disease (34 T1N0 and 89 T2N0) (see table 1 for explanation of classification) with a mean age of 64.8 years (range 39–82). Pneumonectomy was performed in 27 patients (five for T1N0 and 22 for T2N0) while lobectomy was

Table 1 New international TNM staging system

Stage	*T*	*N*	*M*
I	T1	N0	M0
	T2	N0	M0
II	T1	N1	M0
	T2	N1	M0
IIIa	T3	N0	M0
	T3	N1	M0
	T1–3	N2	M0
IIIb	Any T	N3	M0
	T4	Any N	M0
IV	Any T	Any N	M1

Primary tumour (T)
T1 = A tumour that is 3.0 cm or less in greatest dimension, surrounded by lung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronschoscopy.
T2 = A tumour more than 3.0 cm in greatest dimension, or a tumour of any size that invades the visceral pleura or has associated atelectasis or obstructive penumonitis extending to the hilar region. At bronchoscopy the proximal extent of demonstrable tumour must be within a lobar bronchus or at least 2.0 cm distal to the carina. Any associated atelectasis or obstructive pneumonitis must involve less than an entire lung.
T3 = A tumour of any size with direct extension into the chest wall, diaphragm or the mediastinal pleura or pericardium without involving the heart, great vessels, trachea, oesophagus or vertebral body, or a tumour in the main bronchus within 2 cm of the carina.
T4 = A tumour of any size with invasion of the mediastinum or involving heart, great vessels, trachea, oesophagus, vertebral body or carina or the presence of malignant pleural effusion.
Node involvement (N)
N0 = No demonstrable metastasis to regional lymph nodes.
N1 = Metastasis to lymph nodes in the peribronchial or ipsilateral hilar region, or both.
N2 = Metastasis to ipsilateral mediastinal and subcarinal lymph nodes.
N3 = Metastasis to contralateral mediastinal or hilar lymph nodes or to ipsilateral or contralateral scalene or supraclavicular lymph nodes.

Table 2 Histological classification of 200 patients

Stage	*Squamous carcinoma*	*Adenocarcinoma*	*Large cell*	*Small cell*	*Bronchus/ alveolar*	*Total*
I	75	38	6	4	0	123
II	23	10	5	1	1	40
IIIa	22	13	0	2	0	37
Total	120	61	11	7	1	200

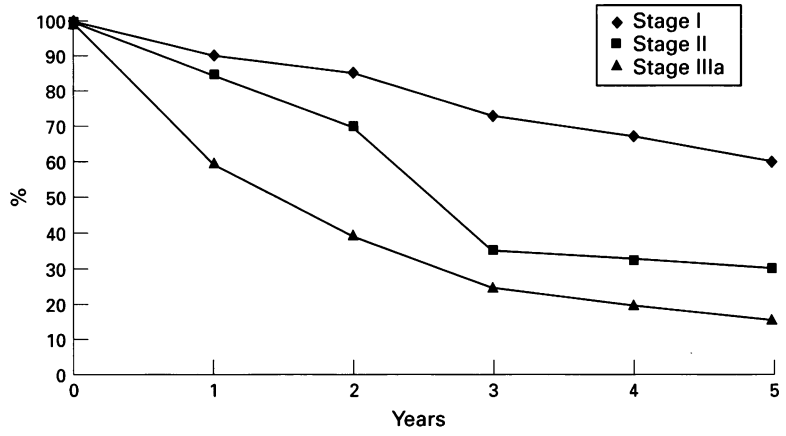

Figure 1 Survival curves in patients with stage I, II and IIIa lung cancer.

performed in 96 (29 for T1N0 and 67 for T2N0). Twenty three patients (19%) were asymptomatic; in those with symptoms cough (64%) and haemoptysis (49%) were the most common complaints. Forty patients (31 men) with a mean age of 61.4 years (range 40–83) had stage II disease (eight T1N1 and 32 T2N1) and 37 patients (28 men) with a mean age of 65 years (range 54–74) had stage IIIa disease.

The histological classification of each stage is shown in table 2. N2 disease was diagnosed postoperatively (from the pathological specimen) in 28 cases of which 14 were squamous cell, 12 adenocarcinomas, and two small cell carcinoma. The small number of patients with small cell carcinoma (n=7) who underwent surgery did so either because they were known to have stage I disease, or the histology was unknown at the time of operation, or the cell type of the preoperative biopsy specimen proved to be incorrect.

All patients were assessed preoperatively by computed tomographic (CT) scans or mediastinal exploration with lymph node biopsy, or both. No patients with preoperatively proven N2 disease or stage IIIb disease underwent surgery. Posterolateral thoracotomy was the standard method of surgical access and the extent of resection was dictated by operative findings. Formal clearance of all mediastinal lymph nodes was not undertaken but it was standard practice to resect any abnormal looking nodes and routinely to sample nodes immediately proximal to the resection margin – for example, interlobar nodes at lobectomy and subcarinal and paraoesophageal nodes at pneumonectomy. Sixteen of the 57 pneumonectomies required intrapericardial dissection. Lobectomy with chest wall resection was performed in six patients with stage IIIa disease and sleeve lobectomy was necessary in three cases.

No protocol for preoperative or postoperative adjuvant therapy was in operation at the time of this study. Some patients with stage IIIa disease were referred for postoperative radiotherapy either because of chest wall or mediastinal lymph node invasion, but this was at the discretion of the operating surgeon.

Complete follow up was available for all patients for 60 months.

STATISTICAL METHODS

All values are represented as means and survival analysis was calculated using the Kaplan-Meier product limits method with 95% confidence interval for survival function. The log rank test was used to calculate the difference between survival curves. The Student's *t* test was used to test the difference between groups, a p value of <0.05 being considered significant.

Results

In the 123 patients with stage I disease the three and five year survivals were 72.5% (95% CI 64.3% to 80.7%) and 59.4% (95% CI 50.8% to 68%), respectively (fig 1). No significant difference in survival was noted between patients with T1 (n=34) and T2 (n=89) disease, but the five year survival in these groups was 68% and 58%, respectively. Patients with squamous carcinoma had a five year survival of 69.4% compared with 52.6% for those with adenocarcinoma, but this again was not significant (p=0.1). In this group age, sex, and extent of resection made no difference.

In the 40 patients with stage II disease the three and five year survivals were 32.5% (95% CI 18.7% to 47%) and 30% (95% CI 15.9% to 44.1%), respectively. Patients with stage II disease with T1N1 lesions had a five year survival of 50% (95% CI 37.3% to 62.9%) which was significantly better than patients with T2N1 lesions who had a five year survival of 28.1% (95% CI 16.9% to 39.3%, p=0.01; fig 2). The difference in survival between these groups was therefore 21.9% (95% CI 5% to 38.8%). Cell type, age, sex, and extent of resection were again insignificant.

Patients with stage IIIa disease (n=37) had a five year survival of 16.2% (95% CI 3.5% to 31%). In the 28 patients with N2 disease the three and five year survivals were 21.4% and 14.3%. Although this was poorer than for patients with no N2 nodes (27.3% and 17.2%), the numbers were small and the differences did not reach significance (p=0.8). Cell type, sex, and extent of resection were insignificant.

In the whole patient population 60% had squamous carcinoma and 30% adeno-

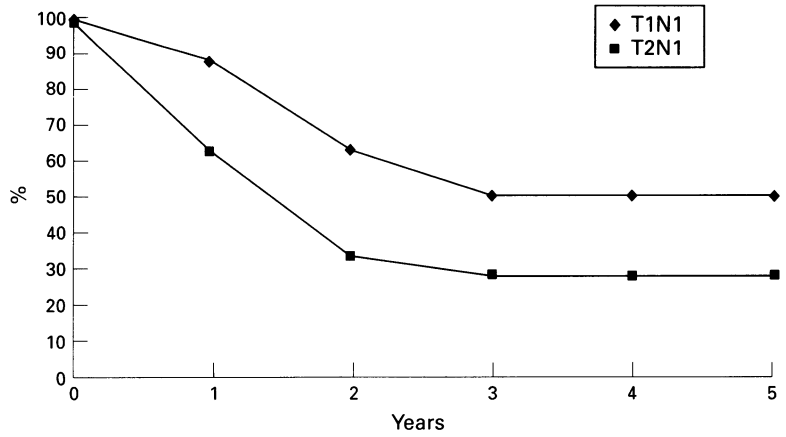

Figure 2 Survival curves within stage II lung cancer for patients with T1N1 and T2N1 tumours.

carcinoma. There was a difference in five year survival of 52% versus 38% but, as in individual stages, this was not significant. Two of the four patients with stage I small cell carcinoma were alive and well at five years, but the other five died within two years. There were 41 patients over the age of 70 with an overall five year survival of 46.3%. This was similar to the 45.5% five year survival in the 159 patients who were aged under 70. In patients with stage IIIa disease, however, none of the eight patients aged over 70 survived more than 24 months. Three died of local recurrence, two of metastatic disease, and three from unrelated causes.

Discussion

The new TNM staging system for lung cancer has been shown to be an accurate predictor of prognosis. In this study survival rates for all three stages of operable cancer were similar to those in other large studies from different countries.[1 2] These figures therefore broadly support the logic of dividing patients into the stages currently used. The question remains, however, as to whether different prognostic groups exist within these stages. We found no difference in survival between patients with T1 and T2 tumours within stage I, but others have suggested that it should be subdivided into stages Ia and Ib.[3] On the other hand, we found a significant difference in survival within stage II between patients with T1N1 and T2N1 tumours which has not previously been noted. The most controversial aspect to date of the current staging system has been the inclusion of patients with large locally invasive tumours without mediastinal lymph node involvement alongside patients with N2 disease in stage IIIa. In our study, as in others, the former group did better, but numbers were small. In other studies long term survival in this group has ranged from 6% to 30%.[4 5] These data raise the possibility that stage IIIa, as it is currently constructed, is a heterogeneous entity.

Another controversy surrounding the significance of ipsilateral mediastinal node involvement (N2 disease) relates to the observation that patients with disease discovered at operation fare better than those in whom the nodes are shown to be involved at preoperative staging.[6 7] We, like others, have followed the empirical practice of trying to exclude patients with N2 disease by preoperative staging but, when involved nodes are encountered at operation, we carry out as extensive a lymphadenectomy as possible in the belief that it remains the best chance of cure.[8 9]

The possibility of the addition of adjuvant or neoadjuvant therapy to surgery in patients with N2 disease is the subject of a number of recent and current studies. It has been suggested that adding adjuvant therapy improves survival and that adding neoadjuvant therapy can "down stage" disease to render surgical cure more likely.[10-13] Both these hypotheses will probably require prospective randomised multicentre if not multinational trials to test them properly, but they are the most encouraging possibilities for improving cure rates in lung cancer currently available.

Postoperative radiotherapy was given to a small number of patients in this study on an ad hoc basis but no conclusions could be drawn about its efficacy. Some authors have suggested a survival benefit from postoperative radiotherapy for patients with N2 disease[14] but a recent Medical Research Council trial did not confirm this.[15]

The aim of surgery in this study was to achieve cure by the safest and most conservative procedure possible. There were no differences in long term survival between patients who had lobectomy and those who had pneumonectomy indicating, as others have found, that performing surgery more radical than that required to clear the tumour confers no benefit.[7 16] In the short term, however, pneumonectomy was a more dangerous procedure with a higher mortality. Although increasing age as a risk factor after surgery has been a subject for concern,[17] recent studies have indicated that surgical resection is safe in carefully selected patients who are aged over 70.[18 19] The importance of selection in this group is important, however, and, while age was not a risk factor overall in this study, patients over 70 with stage III disease all died within two years.

We conclude that radical resection with the aim of surgical cure is the best available treatment for patients with stages I and II lung cancer and still offers a better chance of cure than any other treatment for patients with stage IIIa disease. The theory that survival in this group might be improved by adjuvant therapy needs to be explored further but is as yet unproven. This study also suggests that there might be a case for subdividing patients with stage II disease according to tumour size and that resection of locally advanced disease in the elderly may not be justified.

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