Pneumonectomy for non-small cell lung cancer: predictors of operative mortality and survival

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Abstract

Objective: The purpose of this study was to identify predictors of operative mortality and survival following pneumonectomy for non-small cell lung cancer (NSCLC).

Methods: All 206 patients having a pneumonectomy for NSCLC between 1991 and 1997 in our unit were prospectively studied. There were 162 males (79%) and 44 females (21%) with a mean age (± standard deviation) of 61 ± 7.7 years (range 34–81 years). Squamous cell (75%) and adenocarcinoma (17.0%) were the predominant histological types. The possible impact of 29 parameters on operative mortality and survival was tested with univariate and multivariate analysis. The mean follow-up was 2.3 ± 1.2 years, ranging between 0 and 6.8 years, and it was complete.

Results: Operative mortality was 6.8% (14 deaths). On multiple logistic regression older age (P = 0.04) and the development post-operatively of bronchopleural fistula (BPF) (P = 0.01) were independent predictors of operative mortality. The overall, Kaplan–Meier, 1-, 3- and 5-year survival (± standard error from the mean), inclusive of operative mortality, was 68 ± 3.3, 42 ± 4.1 and 35 ± 4.5%. On Cox proportional hazards regression adenocarcinoma (P = 0.006), the development of BPF (P = 0.003), older age (P = 0.03) and higher pathological stage (P = 0.02) were independent adverse predictors of survival.

Conclusion: Pneumonectomy for NSCLC carries a considerable, but acceptable, operative mortality and provides an important survival benefit. This study suggests that older age and BPF are major determinants of an unfavourable in-hospital outcome; older age, BPF, adenocarcinoma cell type and higher pathological stage significantly reduce the probability of a long-term survival.

Keywords: Pneumonectomy; operative mortality; survival

1. Introduction

Carcinoma of the lung is the most common cause of cancer death in the Western world [1].

Small cell lung cancer is managed mainly with chemotherapy and/or radiotherapy but resectional surgery provides a real hope of cure for patients with non-small cell lung carcinoma (NSCLC).

Although preservation of lung parenchyma is desirable, complete removal of the affected tissues may necessitate a pneumonectomy. Removal of the entire lung carries a higher operative mortality than lesser lung resections [2] but the increased operative risk ought to be balanced against the anticipated survival benefits.

Several studies have, previously, examined the impact of various factors on the early and late outcome following lung resection for NSCLC [2–14], but few of them have analysed cohorts of patients undergoing a pneumonectomy [11–14].

The purpose of this study was to identify predictors of operative mortality and survival following pneumonectomy for primary bronchogenic, non-small cell lung cancer (NSCLC) within a single unit.

2. Patients and methods

Between 1991 and 1997, 682 consecutive patients were submitted to a thoracotomy with a view to performing lung resection. Three hundreds and fifty-three (52%) underwent a lobectomy or lesser resections, 42 (6%) had a bilobectomy and 212 (31%) had a pneumonectomy (206 of them for NSCLC). In 75 (11%) patients a lung resection was not performed.

The 206 patients who underwent a pneumonectomy for NSCLC are the subjects of our study. There were 162 males (79%) and 44 females (21%) with a mean age of 61 ± 7.7 years (range 34–81 years).
2.1. Preoperative evaluation

Preoperative evaluation was by means of physical examination, haematological and biochemical investigations, chest X-ray, electrocardiogram, computerised tomography of the chest and abdomen and bronchoscopy. Additional investigations such as liver ultrasound, bone scan, head CT etc. were performed if required on the basis of clinical findings and/or laboratory parameters (e.g. abnormal liver enzymes or serum calcium, skeletal symptoms, hepatomegaly, splenomegaly, lymphadenopathy, abnormal neurological examination etc.).

Cervical mediastinoscopy and anterior mediastinotomy are important diagnostic and staging procedures in patients having mediastinal lymph nodes greater than 1 cm on the CT scan but not all surgeons used them routinely over the study period. Currently, however, they are invariably employed where indicated.

All patients had spirometry and arterial blood gases. In patients with borderline predicted postoperative lung volumes a ventilation perfusion isotopic scan, was, also, performed. Exercise tests were carried out in patients above the age of 70 years, those with lung volumes of less than 60% of predicted value for age and height or those with previous history of cardiovascular disease and/or ischaemic changes on the ECG (Q waves, ST wave depression, left ventricular hypertrophy, complete right bundle branch block, premature ventricular contractions etc.). Patients exhibiting an abnormal exercise test, were referred to the cardiologists for further evaluation.

Patients were considered for pneumonectomy if there was no evidence of mediastinal involvement by the tumour or distant metastatic disease and they were deemed as having adequate cardiac reserve and a predicted postoperative FEV1 of at least 1l, as assessed by preoperative spirometry and/or ventilation/perfusion isotopic scan.

2.2. The operation

The operative approach consisted of a standard pneumonectomy with block dissection of hilar nodes and sampling of mediastinal lymph nodes as appropriate. Formal mediastinal lymph node clearance was not performed. One hundred and four patients (5.3%) were diabetic.

The mean body mass index was 24.5 and the mean FEV1/FEV1 ratio was 0.66. Eleven patients having a FVC of at least 1l, as assessed by preoperative spirometry and/or ventilation/perfusion isotopic scan, were referred to the cardiologists for further evaluation. All patients had spirometry and arterial blood gases. In patients with borderline predicted postoperative lung volumes a ventilation perfusion isotopic scan, was, also, performed. Exercise tests were carried out in patients above the age of 70 years, those with lung volumes of less than 60% of predicted value for age and height or those with previous history of cardiovascular disease and/or ischaemic changes on the ECG (Q waves, ST wave depression, left ventricular hypertrophy, complete right bundle branch block, premature ventricular contractions etc.). Patients exhibiting an abnormal exercise test, were referred to the cardiologists for further evaluation.

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2.3. Data collection and follow-up

Patients were subjected to outpatient review every 3 months for the first year, every 6 months for the next 2 years and yearly thereafter. Survival time was calculated from the time of the operation until death or until the end of the study period.

Data was obtained from the thoracic surgery audit database, entered in a prospective systematic fashion by a dedicated Thoracic Surgery Data Manager. Complete survival information (up to death or date last seen) was available in 100% of patients. The mean follow-up was 2.3 ± 1.2 years, ranging between 0 and 6.8 years with a total of 505.7 patient years.

2.4. Definitions and statistics

Operative morbidity and mortality includes any morbid event and death, taking place within 30 days from the operation or during the same hospital admission.

Continuous data are presented as means (± standard deviation) and categorical variables as percentages.

Twenty-nine variables (Appendix) were tested with univariate analysis with end points being operative mortality and survival.

Continuous variables were screened with logistic regression, means were compared with unpaired t-test and proportions with Chi-square or Fishers exact test as appropriate. The prediction of freedom from late events (± standard error from the mean) was estimated with the Kaplan–Meier product limit method and the resulting curves compared with the log-rank test.

The variables which attained a P value of less than or equal to 1.0 on univariate analysis, were entered into multiple logistic stepwise regression analysis and Cox proportional hazards regression models. A P value of <0.05 was considered statistically significant. Statistical analysis was done using the statistical package SPSS PC (version 8.0) (Chicago, IL, 60611).

3. Results

3.1. Main preoperative clinical features

Sixty-seven patients (33%) had a previous history of cardiovascular disease (i.e., ischaemic heart, disease, hypertension, myocardial infarction, deep venous thrombosis, pulmonary embolism) 21 patients (10%) had pre-existing respiratory disease (i.e. chronic obstructive Airways disease, asthma, restrictive lung disease, tuberculosis) and 11 patients (5.3%) were diabetic.

The mean FEV1 was 2.16 ± 0.45 l/s (1.05–4.3 l/s) with 41 (20%) patients having a FEV1 < 60% of the predicted value. The mean FVC was 3.26 ± 0.65 l (1.45–6.15 l) with 17 patients having a FVC < 60% of the predicted value, and the mean FEV/FEV1 ratio was 0.66 ± 0.07 (0.36–0.90). The mean body mass index was 24.5 ± 3.1 (13.4–34).
3.2. Histology and pathological staging

Squamous cell carcinoma was the commonest cell type being present in 155 patients (75%). Other cell types were adenocarcinoma in 35 (17.0%), large cell carcinoma in 12 (5.8%) and other cell types in four patients (1.9%).

Histopathological examination of the resected specimens demonstrated the presence of stage I disease in 64 (31%) patients, stage II disease in 76 (37%) and stage IIIa disease in 66 (32%) patients.

3.3. Operative morbidity and mortality

Operative mortality (30 day plus in-hospital mortality) was 6.8% (14 patients). The causes of death were the development of bronchopleural fistula (BPF) in four, pneumonia in four, myocardial infarction in three, pulmonary embolism in two and intra-operative haemorrhage in one patient.

A total of 82 patients (39%) experienced early postoperative complications. These were respiratory complications in 23 (11%), cardiovascular complications (other than supra-ventricular tachycardias) in nine (3.9%), supraventricular tachycardias-mostly atrial fibrillation- in 36 (17%), and other complications in nine (3.9%) patients.

3.4. Bronchopleural fistula

Bronchopleural fistula occurred in 14 patients at a mean time of 41.6 ± 36.6 days (range 4–214 days). In four cases it was diagnosed within 14 days of the operation, in six cases within 30 days and in four cases later. Bronchopleural fistula was more prevalent following right pneumonectomy than after left pneumonectomy (10 patients, 9.8% vs four patients, 3.8%). The patients in whom the main bronchus was simply stapled appeared more likely to develop a BPF than those having their bronchial stump covered with a pleural flap (11 patients, 9.8% vs three patients, 3.2%). These differences, however, did not reach statistical significance ($P = 0.1$ and $P = 0.09$, respectively).

Development of BPF ($P = 0.002$), older age ($P = 0.01$) and male gender ($P = 0.04$) were significant univariate factors for operative mortality. On multiple logistic regression, BPF ($P = 0.01$) and older age ($P = 0.04$) were independent predictors of operative death.

3.5. Late survival

Kaplan–Meier survival at one, three and five years, inclusive of operative mortality, was 68 ± 3.3, 42 ± 4.1 and 35 ± 4.5% (Fig. 1). Adenocarcinoma ($P = 0.01$), BPF ($P = 0.001$), higher pathological stage ($P = 0.02$), older age ($P = 0.02$), higher preoperative levels of plasma urea ($P = 0.006$) and lower FEV1/FVC ratio ($P = 0.02$) were significant adverse univariate factors for overall survival.

On Cox proportional hazards regression model adenocarcinoma ($P = 0.006$) (Fig. 2), BPF ($P = 0.003$) (Fig. 3), higher pathological stage ($P = 0.02$) (Fig. 4) and older age were independent adverse predictors of overall survival.

4. Discussion

Anatomic lobectomy with mediastinal nodal staging is the present standard of care for patients with peripheral stage I or stage II non-small cell lung cancer. However, anatomic site or extent of the tumour may make pneumonectomy necessary. Knowledge that the operative risk of pneumonectomy is greater than that of lobectomy and that the late survival is similar following any of these procedures [2], has led to a decline in the frequency of pneumonectomy. In a recent study the proportion of pneumonectomies has fallen from 46% of all lung cancer resections in 1980 to 36% in 1996 [16], a trend reflected in our own practice.

The operative mortality of 6.8% among our patients was acceptable, being similar to early death rates 5.3–12.8%
reported from elsewhere [2,5,11–14]. Older age and the development of BPF were independent risk factors for operative mortality in this series. Older age was an important risk factor for early death following lung resection for cancer in early [17,18] and more recent studies [3,10]. Studies on cohorts of patients undergoing pneumonectomy for carcinoma have produced conflicting results. In some reports, older age has increased considerably the operative risk [8,13] whereas in others [6,11,12,14] older patients were as likely to die following their pneumonectomy as were their younger counterparts. These differences may well reflect the diversity in the make up of the patients involved in these studies and comparisons between studies should be undertaken cautiously [19]. Our analysis, nevertheless, suggests that with increasing age, despite careful patient selection, pneumonectomy does become a more hazardous procedure [19].

The incidence of BPF of 6.8% in this series was similar to the 6–7% reported by Patel et al., [11] and it is higher from a BPF rate as low as 1.5% reported by Al-Kattan et al. [20]. BPF is a major, life-threatening complication and it is, thus, not surprising that it emerged as an independent risk factor for operative death in this study. Similar experience following elective pneumonectomy has been previously described [11].

Contrary to previous reports [5,11], we found neither poor forced expiratory volume in 1 s (FEV1) alone or as ratio with forced vital capacity (FEV1/FVC) nor the co-existence of cardiovascular conditions to independently predict operative mortality after pneumonectomy [2,11]. Diffusing lung capacity, exercise capacity and oxygen consumption have been, also, shown to be important predictors of early death and pulmonary morbidity [10,21,22] but these measures were not routinely used during the period of this study.

The overall 5-year survival, inclusive of operative mortality, was 35%. In most of the previously published series, older age has not been associated with poorer long-term survival following lung cancer resections [11–14]. Older age, however, was identified as an independent adverse predictor of late survival in our study, a finding similar to that recently reported in a population based study for patients undergoing a lung resections for NSCLC from Geneva [3]. In another report from Chicago [10] older age alone was, also, a negative independent predictor of late survival with a relative death rate of 1.31 per 10-year increase in age.

In addition to increasing the operative mortality, the development of a BPF had an unfavourable effect on the long-term survival among our patients presumably as a result of chronic sepsis and debilitation (Fig. 3). Patients having adenocarcinoma cell type fared considerably worse in this series, indeed adenocarcinoma cell type was an independent predictor of a poorer survival (Fig. 2). Several previous authors failed to demonstrate an effect of histological cell type but others did identify a clear survival benefit in favour of the patients having squamous cell carcinoma. We agree with Kadri and Dussek [4] that the prognostic significance of histological cell type is by itself unclear, but it is of note that where the cell type was shown to have an effect, this has been consistently in favour of the squamous cell type [18,23].

It is well established that the prognosis after resection of lung cancer is directly related to the tumour stage [5,15] although Martini et al. [9] have found that the most important predictor of a 10-year survival was a disease-free survival 5 years following the initial treatment.

We do not undertake formal mediastinal lymph nodal clearance and accept that pathological staging has been sub-optimal in this series, although consistent throughout the study period. It is, therefore, most likely that some tumours were under-staged and this might have affected the survival curves presented in Fig. 4. Despite this inadequacy, pathological stage was an independent predictor of a reduced late survival in this study.
Female gender has been shown by others to exert a positive effect on the long-term survival benefit after resection for NSCLC [24,25], although the explanations on the possible aetiological mechanisms mediating this effect remain speculative. We were unable to demonstrate a gender-based survival benefit in the present study.

5. Conclusions

The analysis of these prospectively collected data demonstrates that older age and bronchopleural fistula are the major determinants of an unfavourable in-hospital outcome whereas adenocarcinoma cell type, higher pTNM stage, older age and bronchopleural fistula considerably reduce the probability of a long-term survival.

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References


Appendix A

A.1. List of variables testedo

Age, gender, squamous cell carcinoma, adenocarcinoma, t-stage, lymph node involvement, pTNM stage, previous history of respiratory disease, previous history of cardiovascular disease, diabetes mellitus, plasma haemoglobin, plasma urea, plasma creatinine, liver function tests (normal or abnormal), FEV1, percentage of the predicted FEV 1, FVC, percentage of the predicted FVC, FEV1/FVC ratio, peak flow, pCO2, pO2, pH, body mass index, side of pneumonectomy (right Vs left), operating surgeon, bronchopleural fistula, other respiratory complications, cardiovascular complications.