Outcome after lung cancer surgery.
Factors predicting early mortality and major morbidity

G. Myrdal\textsuperscript{a,}\textsuperscript{*}, G. Gustafsson\textsuperscript{a}, M. Lambe\textsuperscript{b}, L.G. Hörte\textsuperscript{c}, E. Ståhle\textsuperscript{a}

\textsuperscript{a}Department of Thoracic and Cardiovascular Surgery, Uppsala University Hospital, SE-751 85 Uppsala Sweden
\textsuperscript{b}Department of Medical Epidemiology, Karolinska Institute, Stockholm, Sweden
\textsuperscript{c}Department of Public Health Sciences, Karolinska Institute, Stockholm, Sweden

Received 14 March 2001; received in revised form 2 June 2001; accepted 17 June 2001

Abstract

Objective: This study was undertaken to assess mortality, complications and major morbidity during the first 30 days after lung cancer surgery and to estimate the significance of presurgical risk factors. Methods: The study was based on all patients referred for surgery for primary lung cancer from 1 January 1987 to 1 September 1999. There were in total 616 patients with primary lung cancer. Three-hundred and ninety-four were men and 222 women. Postoperative events studied were divided into major and minor complications or death during the first 30 days after surgery. The significance of risk factors for an adverse outcome (defined as death or major complication in the first 30 days postoperatively) was assessed by uni- and multivariate logistic regression analyses. Results: During the study period an increasing number of women and of patients older than 70 years underwent surgery. Overall 30-day mortality was 2.9, 0.6% after single lobectomy and 5.7% after pneumonectomy. Male gender, smoker, FEV\textsubscript{1}<70% of expected value, squamous cell carcinoma and pneumonectomy were risk factors predicting adverse outcome in the univariate model. Pneumonectomy and FEV\textsubscript{1}<70%, were the only independently significant factors for adverse outcome. Only pneumonectomy was independently associated with an increased risk for early death. Conclusion: Our results show low mortality and morbidity after lung cancer surgery. However, patients with reduced lung capacity and those undergoing pneumonectomy should be treated with great care, as they run a considerable risk of major complications or death during the first 30 days postoperatively. Older age (>70 years) does not appear to be a contraindication to lung cancer surgery, but patients in this group should undergo careful preoperative evaluation. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Lung cancer; Postoperative complications; Pulmonary resections; Operative mortality; FEV\textsubscript{1%}

1. Introduction

Lung cancer is the most common form of cancer worldwide, and the most common cause of cancer death in western countries [1–3]. Radical surgical resection, with or without adjuvant treatment, is still a prerequisite for cure. In spite of different additional modes of treatment, survival is still poor. In European countries the proportion of patients with diagnosed lung cancer who undergo surgery for this disease varies between 10 and 20% [4,5]. Advances in operative and postoperative care have led to a decline in complications and mortality rates during the last two decades [6–9]. But since the proportion of older patients (≥70 years) has increased during this time period, the incidence of associated co-morbidity has increased [10]. To be able to improve the quality of operative procedures and identify patients running the highest risk, and to optimise the patients condition, medication and respiratory status before surgery, it is important to have knowledge of peri- and postoperative mortality and morbidity, and also of risk factors prior to surgery. Furthermore, the operative risks must be considered in relation to the long-term results in order to identify patients who will clearly benefit from surgery.

The aim of the present study was to examine the operative mortality and morbidity after lung cancer surgery and to identify factors associated with an adverse outcome. The study comprised 616 consecutive patients referred to Uppsala University Hospital, from a defined population, during a 12-year period.

* Corresponding author. Tel.: +46-18-6110000; fax: +46-18-551526.
E-mail address: gunnar.myrdal@thorax.uu.se (G. Myrdal).

1010-7940/01/$ - see front matter © 2001 Elsevier Science B.V. All rights reserved.
PII: S1010-7940(01)00875-2
2. Material and methods

2.1. Patients

The study comprised only patients with a primary malignancy of the lung or pleura. During the study period, January 1987 to September 1999, 619 surgical procedures for primary carcinoma of the lung or pleura were performed at the Department of Thoracic and Cardiovascular Surgery, University Hospital, Uppsala, Sweden. Three patients living outside Sweden were lost to follow-up. The remaining 616 patients formed the basis of this study.

The mean age at surgery was 63.8 years (23.9–81.8 years). There were 394 men (mean age 65.1 years (34.7–81.8)) and 222 women (mean age 61.6 years (22.9-81.7)). All patients underwent preoperative CT scan of the thorax and upper abdomen or ultrasound of the upper abdomen. If there were any signs of metastatic spread to the mediastinum (lymph nodes >1.5 cm), mediastinoscopy was performed as routine. If cancer spread was found in the mediastinum at mediastinoscopy (N3 or N2), no further surgical procedure was carried out. Eight patients received a neoadjuvant therapy. At all operations the standard open postero-lateral thoracotomy approach was used. One surgeon performed 60% (368) of the operations and assisted at 110 of the remaining 248. A team of physiotherapists provided pre- and postoperative respiratory assistance. Patient’s characteristics are presented in Table 1.

2.2. Outcome, data collection and follow-up

Early death was defined as death from any cause within 30 days of surgery. Complications were classified as minor or major (i.e. potentially life-threatening event), occurring within the first 30 postoperative days (Table 2). An adverse outcome was defined as a major complication or death within the first 30 days after surgery.

Patients eligible for inclusion were identified from an in-
patients died during the first 30 days to allow an interaction analysis taking into account early death.

For comparisons between groups, such as rate of atrial fibrillation and the incidence of major complications in relation to surgery the $\chi^2$-test was used.

All statistical calculations were performed with the SAS 6.12 statistical procedure (SAS Institute).

### 3. Results

#### 3.1. Early mortality (within 30 days) after lung cancer surgery

Eighteen patients (2.9%) of the 616 patients undergoing surgery died within 30 days (Table 1). Fourteen (78%) of these 18 patients also experienced a major complication. Nine patients had respiratory failure after surgery, which led to death. In four cases, perioperative bleeding or bleeding soon after the operation was considered to be the main cause of death (Table 2).

Early mortality was unchanged over time (Table 1). Early mortality was higher in relation to pneumonectomy (5.7%) as compared to less extensive surgery such as lobectomy (0.6% for single lobectomy) (Table 1).

One hundred and forty-two patients (25%) had an FEV$_1$ lower than 70% of the expected, and the early mortality in this group was 4.2%. 133 (94%) of those with a low FEV$_1$ ($\leq$70%) were former or current smokers, in one case, smoking habits were not known. In one cases of eleven, bronchopleural fistulas was related to death.

#### 3.2. Complications after lung cancer surgery

Major complications occurred in 54 patients (8.8%) (Table 1). The early mortality among those who experienced a major complication was 26%, compared to 0.7% among those with an uneventful postoperative course. The frequency of major complications was higher after pneumonectomy (18.5%) than after lobectomy (5.7%) ($P = 0.001$) (Tables 1 and 3). In overall terms, serious bleeding occurred in 3.2%, 7.6% in relation to a pneumonectomy and 1.6% after lobectomy. Respiratory failure occurred in 2.8%, in 6.4% after pneumonectomy and in 1.5% after lobectomy. Postoperative bleeding leading to re-exploration was seen after twenty procedures (3.2%), three of them lead to death. (suture insufficiency in the pulmonalis arteries or veins). In the remaining 17 the most frequent causes of bleeding was from bronchial arteries (12), pulmonalis arteries (2) and unknown sites (3).

Postoperative atrial fibrillation occurred in 11.5% (71/616) of all cases and tended to be more common after pneumonectomy (15.3%, 24/157) but not significantly so ($P = 0.08$). To reduce the risk of postoperative atrial fibrillation, more than two-thirds (106/157) of the patients who underwent pneumonectomy had been treated prophylactically with digoxin. However, digoxin treatment did not

### Table 2

<table>
<thead>
<tr>
<th>Events</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor complications</td>
<td></td>
</tr>
<tr>
<td>Non-life-threatening disorders</td>
<td>137</td>
</tr>
<tr>
<td>Supraventricular arrhythmia$^a$</td>
<td>71</td>
</tr>
<tr>
<td>Continuous air leakage</td>
<td>24</td>
</tr>
<tr>
<td>Antibiotics other than prophylaxis</td>
<td>21</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>8</td>
</tr>
<tr>
<td>Obstructive symptoms</td>
<td>7</td>
</tr>
<tr>
<td>Paralysis of recurrent nerve</td>
<td>3</td>
</tr>
<tr>
<td>Insufficient wound healing</td>
<td>2</td>
</tr>
<tr>
<td>Diaphragmatic paresis</td>
<td>1</td>
</tr>
<tr>
<td>Major complications</td>
<td></td>
</tr>
<tr>
<td>Life-threatening disorders</td>
<td>54</td>
</tr>
<tr>
<td>Postoperative bleeding$^b$</td>
<td>20</td>
</tr>
<tr>
<td>Respiratory failure$^c$</td>
<td>17</td>
</tr>
<tr>
<td>Bronchopleural fistulas$^d$</td>
<td>11</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>2</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1</td>
</tr>
</tbody>
</table>

$^a$ ECG was recorded in all patients with clinical signs of atrial fibrillation such as palpitations, chest discomfort and nausea.

$^b$ Defined as more than 24 h of mechanical respiration, reintubation, ARDS or pneumonia.

$^c$ In ten cases right side (eight pneumonectomies), one left sided lobectomy (upper lobe).
affect the occurrence of this complication; the proportion of treated and untreated patients who suffered atrial fibrillation were 15% (16/106) and 19% (8/43) respectively ($P = 0.64$).

The incidence rates of major complications in relation to patient characteristics are shown in Table 1.

### 3.3. Risk factor analysis

#### 3.3.1. Early mortality

Pneumonectomy was the only variable that was significantly associated with early mortality (OR, 3.0; CI, 1.2–7.8).

#### 3.3.2. Adverse outcome (death or major complication)

A total of 58 patients either experienced a major complication or died within 30 days (54 experienced major complications and four died during the first 30 days without a major complication), fulfilling the criteria for an adverse outcome. Male sex, pneumonectomy, squamous cell cancer, smoking and low a FEV$_1$ ($\leq 70\%$) were associated with an increased risk of an adverse outcome in the univariate analyses (Table 3). However, reduced FEV$_1 \%$ and pneumonectomy were the only factors that were independently associated with an increased risk of an adverse outcome (Table 3).

 Patients with FEV$_1 \leq 70\%$ of the expected who underwent pneumonectomy had an increased risk for adverse outcome (OR, 3.6; CI, 1.5–8.5), whereas reduced FEV$_1 \leq 70\%$ had less influence in those treated with other surgical procedures than pneumonectomy (OR, 1.9; CI, 0.8–4.5). Introduction of an interaction variable showed significant interaction between type of surgery and reduced FEV$_1$ ($\leq 70\%$) ($P = 0.004$).

Ninety per cent of the patients who underwent lobectomy and experienced an adverse outcome had shown a reduced FEV$_1$, i.e. 70% or lower of the expected, before surgery. The corresponding proportion of patients who underwent pneumonectomy was 70%.

### 4. Discussion

This study can be viewed as population-based study, as all patients within a defined geographical area eligible for surgery for primary lung cancer were referred to our clinic.

Our results confirm that low mortality and an acceptable level of major morbidity can be achieved after surgical resections for lung cancer, especially after single lobectomies.

An overall early mortality rate of 2.9% is comparable to the results reported by other investigators [4,6,8,12–18]. There has been some variation between studies, from 2 to 12%, which can partly be explained by the use of different definitions of early death. The lowest death rates reported after lung cancer surgery have usually referred to in-hospital death, in a selected population.

As expected, the mortality was higher following pneumonectomy than after less extensive surgery. Our early mortality rate of 5.7% after pneumonectomy may be compared with figures of 3.2–11.5% in recent reports [6,15–19]. The finding of an early mortality of 0.6% after single lobectomy in our study is low in comparison with other reported figures, which usually range from 1.2–4% [6,17,19].

When frequencies of complications are compared, it must be taken into account that the differences can be partly explained by the criteria used to define complications.

---

**Table 3**  
Risk factors related to early death or other major complications in uni- and multivariate logistic regression

<table>
<thead>
<tr>
<th>Gender</th>
<th>Total no. of patients</th>
<th>Adverse outcome</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Female</td>
<td>222</td>
<td>10</td>
<td>4.5</td>
<td>ref.</td>
</tr>
<tr>
<td>Male</td>
<td>394</td>
<td>48</td>
<td>12.2</td>
<td>2.9</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>459</td>
<td>28</td>
<td>6.1</td>
<td>ref.</td>
</tr>
<tr>
<td>Yes</td>
<td>157</td>
<td>30</td>
<td>19.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Squamous cell cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>341</td>
<td>23</td>
<td>6.7</td>
<td>ref.</td>
</tr>
<tr>
<td>Yes</td>
<td>275</td>
<td>35</td>
<td>12.7</td>
<td>2.0</td>
</tr>
<tr>
<td>Smoking habits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>87</td>
<td>2</td>
<td>2.3</td>
<td>ref.</td>
</tr>
<tr>
<td>Current or former smoker</td>
<td>523</td>
<td>52</td>
<td>9.9</td>
<td>5.5</td>
</tr>
<tr>
<td>Measurement of lung involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV$_1$ &gt;70%</td>
<td>437</td>
<td>29</td>
<td>6.6</td>
<td>ref.</td>
</tr>
<tr>
<td>FEV$_1$ ≤70%</td>
<td>142</td>
<td>24</td>
<td>17</td>
<td>2.9</td>
</tr>
</tbody>
</table>

---

*a* Adverse outcome is defined as a major complication or death within 30 days after the operative procedure.  
*b* Odds ratio.  
*c* Confidence interval.
Using a similar definition for major complications to those applied in other studies [6,10,19] where figures of 12.4% (all procedures) and 17% (pneumonectomy) were obtained [14,20], we found an 8.8% overall incidence of such complications, compared with rates ranging between 12 and 34% in other reports [9,12,14,20,21]. The major complications most often related to a postoperative death were respiratory failure and other related lung complications (9/18), in accordance with other reports [21].

In several studies risk factors for major complications after lung resections have been identified, namely: age, male sex, pneumonectomy, FEV\(_1\), and previously defined concomitant disease [12–14,20]. The sample sizes in most of these studies have been too small to assess allow assessment of risk factors. We evaluated the significance of a number of preoperative variables, based on a substantial number of patients, as indicators of a risk for major complications or death. However, the statistical power depends not only on the sample size but also on the number of patients that fulfil the criteria used to define the endpoint. The excellent results in this study therefore reduced the possibilities of identifying important risk factors. As only a very small number of patients died within 30 days of surgery, this consideration is especially important in attempts to identify characteristics related to increased early mortality. The use of the composite endpoint early death or major complication allowed factors related to an early adverse outcome to be identified with sufficient reliability.

The risk of early death after surgery was twice as high among men as among women. Smokers also ran an increased risk in relation to surgery [19]. In some studies [13,14], but not all [8–10,22], it has been found that advanced age is an important risk factor for early death. In the present study, however, increased age was not a strong risk factor for early mortality. These findings support the view that surgical treatment should also be considered in older patients. Furthermore, previous studies have indicated that concomitant diseases such as ischaemic heart disease, diabetes mellitus or chronic obstructive lung disease represent significant risk factors for an adverse outcome [13]. This was not confirmed in the present study, but it cannot be ruled out that this lack of influence of high age and serious co-morbidity is at least partly due to selection of patients without co-morbidity for surgery. If so, the selection is probably most critical in higher age groups. Nevertheless, old age alone does not appear to be a definite contraindication to surgery.

As confirmed in the present study, a low respiratory capacity, assessed as FEV\(_1\%), appears to be the most important predictor of a high risk of complications after lung resections [23]. In this study, respiratory complications, which were closely related to impaired preoperative pulmonary function, expressed as a decrease in FEV\(_1\%), were associated with approximately 50% of all deaths. We found a significant interaction between type of surgery, namely pneumonectomy, and impaired preoperative pulmonary function. Reduced FEV\(_{1\%}\) was especially unfavourable in patients who underwent pneumonectomy, increasing the risk of death and/or major complications more than three-fold. Some investigators have claimed that predicted postoperatively measured FEV\(_{1\%}\) constitutes a far more reliable risk factor for complications than the preoperative value [12]. It can be assumed that there is a strong correlation between the preoperative and postoperative FEV\(_{1\%}\). However, the finding that impaired pulmonary function is extremely deleterious in patients undergoing a major pulmonary resection supports the notion that the remaining pulmonary capacity is important for the outcome.

The impact of the experience and training of the surgeon has been discussed extensively and is a factor of importance for operative success. In this study, the majority of the procedures were performed by one surgeon. Application of the concept of a single surgeon or a group of surgeons acquiring experience of lung cancer surgery has produced excellent results in this study. Other investigators have observed an increase in complications and mortality rate [24] following operations undertaken by general surgeons without experience of lung surgery. Moreover, excellent results have also been reported in patients with a severely reduced pulmonary capacity, i.e. FEV\(_1\) of less than 1.0 l [18], when surgery has been performed under optimal conditions by experienced surgical teams.

In conclusion, lung cancer surgery appears to be a safe procedure even in elderly patients. Whereas lobectomy was associated with a minimal risk of death or major complications, pneumonectomy was still associated with a substantial risk of an adverse outcome. The majority of patients who died within the first 30 days after surgery also had a major complication. Prevention of complications and improvement of the treatment of patients suffering from major complications are therefore important issues in modern lung cancer surgery.

A reduced respiratory capacity, as reflected by a reduced preoperative FEV\(_{1\%}\) and smoking habits, was the most significant risk factor and was especially harmful in patients undergoing pneumonectomy. On the basis of these findings, patients under consideration for pneumonectomy should be selected precisely and other risk factors should be excluded or neutralised prior to surgery in order to minimise the risk of major complications or death. The importance of assessing lung function prior to surgery should not be underestimated. Measurements of the lung capacity as FEV\(_{1\%}\) appears to be a simple and accurate method for evaluating the risks in patients undergoing lung resections.

Current smokers are a group of patients who run a significant risk of an adverse outcome (major complication or death) after lung cancer surgery. Patients with a history of smoking in combination with a low FEV\(_{1\%}\) could benefit from a preoperative programme for pulmonary rehabilitation. In addition, intensive postoperative care of patients with an impaired pulmonary capacity undergoing extensive surgery may reduce the risks still further.
Acknowledgements

The study was supported by grants from the Uppsala County Association Against Heart and Lung Disease.

References