Does chemotherapy increase the risk of respiratory complications after pneumonectomy?

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Objective: The impact of induction chemotherapy on postoperative complications after pneumonectomy remains unclear. The aim of the study was to test the hypothesis that chemotherapy may increase the risk of postoperative respiratory complications.

Methods: Data from 202 consecutive standard pneumonectomies performed for lung cancer were collected and analyzed. Postoperative and 90-day mortality, overall morbidity, and respiratory complication rates were evaluated in patients who had no induction treatment (group A, n = 103) as well as in those who received it (n = 99, group B). Preoperative chemotherapy was inserted as a variable together with 12 other variables (age, sex, smoking status, body mass index, previous cardiac event, American Society of Anesthesiologists score, preoperative forced expiratory volume in 1 second [percent], diffusion capacity for carbon monoxide adjusted for alveolar volume [percent], side of pneumonectomy, perfusion of the removed lung, operating time, and blood transfusion) into univariate and multivariate logistic regression.

Results. No difference in terms of mortality was recorded between group A (4.9%) and group B (3%, P > .05). Respiratory complications were more frequent in group B than in group A (19 cases, 19.2%, vs 7 cases, 6.8%, P = .008). Univariate logistic regression has demonstrated that pulmonary complications were more frequent in patients over the age of 70 than in those aged 70 or less (25.7% vs 10.2, P = .02), in those with a lower diffusion capacity adjusted for alveolar volume (18.3% vs 5.95%, P = .06), and in patients who received preoperative chemotherapy (19.2% vs 6.8, P = .008). Logistic regression confirmed the role of age (odds ratio = 6.3), preoperative chemotherapy (odds ratio = 4.4), and diffusion capacity adjusted for alveolar volume (odds ratio = 0.33) as risk factors of respiratory complications.

Conclusions. Standard pneumonectomy is a safe procedure even after induction chemotherapy, with a mortality rate in the order of 5%, but this increases in patients over the age of 70 years. In the case of induction chemotherapy, the risk of respiratory complications is significantly increased, apparently not affecting the overall mortality rate.

The first successful pneumonectomy for lung cancer was performed on April 5, 1933, by Evarts Graham for a T2 N1 squamous cell carcinoma.1,2 A few years later, Overholt3 reported a mortality rate of 33.3% after pneumonectomy for malignant disease.

Since then, improvements in surgical techniques as well as in thoracic anesthesia have dramatically improved postoperative mortality, and in 1983 the Lung Cancer Study Group reported an overall mortality rate of 6.2% after pneumonectomy as compared with a mortality of 2.9% after lobectomy.4
The occurrence of respiratory complications is considered to be the most dangerous event after pneumonectomy, because “one-lung” patients are at high risk of respiratory failure when such complications occur.

Whether or not chemotherapy acts as an additional risk factor in respiratory complications is still controversial.4,5 From a theoretical point of view, the impairment of the alveolocapillary membrane, which is expected after chemotherapy,6 could be synergic with other risk factors such as age or fluid overload in causing lung damage.

The general aim of this study was to review our mortality and morbidity rates after standard pneumonectomy, verifying the impact of preoperative chemotherapy on the incidence of respiratory complications.

**Patients and Methods**

**Aim**
The study investigates the validity of the hypothesis that standard pneumonectomy represents a higher risk of postoperative pulmonary complications when performed after induction chemotherapy.

**Population**
The database of the Thoracic Surgery Department of the European Institute of Oncology was reviewed to identify all patients who underwent standard pneumonectomy for lung cancer between January 1998 and August 2005.

Standard pneumonectomy was defined as the intrapericardial or extrapericardial removal of the entire lung, associated with radical mediastinal lymph node dissection without any resection of mediastinal, chest wall, or diaphragmatic structure. Patients who received preoperative radiotherapy were excluded from the study.

Preoperative respiratory function was assessed routinely by blood gas analysis, spirometry, and lung perfusion scan. Intraoperative management was focused on maximally reducing risk of damage to the controlateral lung; fluid administration was in the order of 5 to 7 mL/kg/h crystalloid infusion, not exceeding a total amount of 1500 mL in all cases. Ventilation was managed by a protective-ventilation strategy (a tidal volume ≤ 6 mL/kg, driving pressure < 20 cm H₂O above the positive end-expiratory pressure, permissive hypercapnia, and the preferential use of pressure-limited ventilatory modes).7 Postoperatively, patients had 2 assisted sessions of chest physiotherapy daily starting on the first postoperative day and were asked to repeat the physiotherapy program 6 times during the day until discharge. Amoxicillin–clavulanic acid was administered for the first 5 postoperative days in nonallergic patients.

**Postoperative Complications**
Postoperative death was defined as any death occurring during the postoperative hospital stay or during the first month after surgery; 90-day death was defined as any death occurring within 3 months from the day of pneumonectomy.

Respiratory complications were classified as follows: (1) acute respiratory failure, defined as postoperative ventilator dependence for more than 12 hours or reintubation for controlled ventilation or need of non-invasive ventilation; (2) acute respiratory distress syndrome (ARDS), defined as respiratory failure with acute onset, arterial oxygen tension/fraction of inspired oxygen less than 200 mm Hg, infiltrates seen on chest x-ray film, and pulmonary wedge pressure less than 18 mm Hg; (3) acute lung injury, defined with the same criteria as ARDS but with arterial oxygen tension/fraction of inspired oxygen less than 300 mm Hg; (4) pneumonia, defined by the presence of at least 3 of the following criteria: persistent lung infiltrate on chest x-ray film, fever greater than 38°C, white cell blood count greater than 10,000/mm³ or less than 3000/mm³, purulent secretions, and documented presence of microorganisms on sputum or bronchoaspirate; (5) sputum retention, defined as lobar or whole-lung atelectasis requiring bronchoscopy; (6) pulmonary embolism, documented by lung ventilation/perfusion scintigraphy or angioscan; (7) pulmonary edema, defined as a transient respiratory failure reversed by administration of diuretics; and (8) chronic respiratory failure, defined as the need for continuous oxygen therapy for more than 1 month after discharge.

Other considered complications were cardiac (cardiac rhythm problems, angina, myocardial infarction, cardiogenic shock), surgical (hemothorax, bronchial fistula, empyema, chylothorax, cardial dislocation), and others.

Overall mortality and morbidity and respiratory complication rates were analyzed for the entire population: patients who had received no induction chemotherapy (group A) and patients who had received induction therapy (group B).

**Statistical Analysis**
Group A and group B were compared for all relevant variables, including demographics and all possible risk factors for postoperative complications, using frequency tables for categorical variables and summary statistics (n, mean, median, standard deviation, minimum, and maximum) for continuous variables. The χ² or Fisher exact test was applied where appropriate.

Pulmonary complications and postoperative complications other than pulmonary were considered as outcome variables in a logistic regression model, using the following covariates (risk factors): age, sex, smoking status, body mass index, previous cardiac event, American Society of Anesthesiologists score, preoperative forced expiratory volume in 1 second (percent), diffusion capacity for carbon monoxide adjusted for alveolar volume (Dlco/VA%), induction chemotherapy, side of pneumonectomy, perfusion of the removed lung, operating time, and blood transfusion. Odds ratio (OR) and the corresponding 95% confidence intervals were reported for covariates that were considered clinically relevant or statistically significant at the .05 significance level (Wald χ² test) and then included in the final multivariate model.

**Abbreviations and Acronyms**
- ARDS = acute respiratory distress syndrome
- Dlco = diffusion capacity for carbon monoxide
- Dlco/VA = diffusion capacity for carbon monoxide adjusted for alveolar volume
- OR = odds ratio
TABLE 1. Clinical characteristics of the population

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 202)</th>
<th>No chemo (n = 103)</th>
<th>Chemo (n = 99)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>146</td>
<td>80</td>
<td>79</td>
<td>.71</td>
</tr>
<tr>
<td>Age (y)</td>
<td>62 ± 9</td>
<td>63.5 ± 8.8</td>
<td>60.5 ± 9.1</td>
<td>.08</td>
</tr>
<tr>
<td>Cardiac history</td>
<td>58</td>
<td>27</td>
<td>31</td>
<td>.42</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>79.9 ± 18.8</td>
<td>78.9 ± 19.1</td>
<td>80.9 ± 18.7</td>
<td>.43</td>
</tr>
<tr>
<td>Dlco (%)</td>
<td>68.5 ± 16.7</td>
<td>70.7 ± 18.3</td>
<td>66.4 ± 14.8</td>
<td>.18</td>
</tr>
<tr>
<td>Dlco/VA (%)</td>
<td>87.5 ± 19.5</td>
<td>91.6 ± 19.1</td>
<td>83.4 ± 19.2</td>
<td>.006</td>
</tr>
<tr>
<td>Stage III-IV (stage IV within parentheses)</td>
<td>93</td>
<td>40 (2)</td>
<td>53 (2)</td>
<td>.03</td>
</tr>
<tr>
<td>Right pneumonectomy</td>
<td>96</td>
<td>44</td>
<td>52</td>
<td>.16</td>
</tr>
<tr>
<td>Intrapericardial</td>
<td>63</td>
<td>26</td>
<td>37</td>
<td>.06</td>
</tr>
<tr>
<td>Operating time, min (mean)</td>
<td>144.1 ± 38.8</td>
<td>149.1 ± 38.9</td>
<td>138.9 ± 38.1</td>
<td>.83</td>
</tr>
</tbody>
</table>

P values <.05 are given in bold. FEV1, Forced expiratory volume in 1 second; Dlco, diffusion capacity for carbon monoxide; Dlco/VA, diffusion capacity for carbon monoxide adjusted for alveolar volume.

RESULTS

Population

During the considered period, 202 patients underwent standard pneumonectomy (146 men, median age 63 years). There were 96 right and 106 left pneumonectomies, of which 63 were performed by opening the pericardium. Mean preoperative forced expiratory volume in 1 second was 2.3 ± 0.68 (median of percent of predicted value 80%) and Dlco/VA 1.2 ± 0.38 (87.5%). Preoperative median perfusion of the lung to be removed was 37%, as documented by lung perfusion scan.

One hundred three patients did not receive any chemotherapy before surgery (group A, 51%). Ninety-nine patients (group B, 49%) received preoperative platin-based chemotherapy; 80 of them completed the planned treatment, consisting of 3 or 4 courses of cisplatin and gemcitabine (cisplatinum 80 mg/m² on days 1 and 21; gemcitabine 1250 mg/m² on days 1, 8, and 21). Eleven patients received only 1 or 2 courses of cisplatin and gemcitabine, stopping treatment for toxicity. No significant difference between the 2 groups was evident in terms of age, sex, smoking status, body mass index and American Society of Anesthesiologists score. Group B had a higher incidence of advanced-stage disease than did group A (P = 0.03), mainly because of the higher proportion of patients with stage III disease. Four patients had stage IV disease, 2 in each group. In 3 cases stage IV disease was due to the presence of a single metastatic nodule in another lobe. The fourth patient with stage IV disease had isolated cerebral metastasis treated by surgery and radiotherapy 18 months before pneumonectomy. The mean preoperative Dlco/VA was 91.6% in group A and 83.4% in group B (P = .006, Table 1).

Overall Mortality and Morbidity

Eight patients died in the postoperative period and 1 patient died 6 weeks after discharge (overall mortality 4.5%). Causes of postoperative deaths were ARDS in 3 patients, pneumonia in 2, and acute respiratory failure in 2 patients. One patient died of gastric hemorrhage after 1 month in the intensive care unit. The late death was due to bronchial fistula.

No difference in terms of mortality was recorded between group A (4.9%) and group B (3%, P > .05).

Postoperative complications occurred in 88 patients (43.4%) (Table 2). Sixty-two patients had nonrespiratory complications (atrial fibrillation in 35 patients, bronchial fistula in 11 patients, rethoracotomy for hemothorax in 23 patients, and other complications in 18 patients). The incidence of rethoracotomy because of bleeding was higher in the chemotherapy group (15.1% vs 7.8%, P = .06). No other differences were identified between the 2 groups.

Respiratory Complications

The overall rate of respiratory complications was 12.8% (n = 26). Postoperative mortality in this group was 30.8% (8/26).

Acute respiratory failure requiring reintubation or noninvasive ventilation occurred in 10 patients (4.9%), and chronic respiratory failure requiring oxygen administration after discharge occurred in 6 patients (3%). Other respiratory complications were pneumonia (4 cases), ARDS (3 cases), pulmonary edema (2 cases), pulmonary embolism (1 case), and atelectasis requiring bronchoscopy (1 case).

TABLE 2. Mortality and morbidity by preoperative chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 202)</th>
<th>Chemo (n = 99)</th>
<th>No chemo (n = 103)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>4% (8)</td>
<td>3% (3)</td>
<td>4.9% (5)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Morbidity</td>
<td>44% (88)</td>
<td>50.5% (50)</td>
<td>36.9% (38)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Respiratory</td>
<td>13% (26)</td>
<td>19.1% (19)</td>
<td>6.8% (7)</td>
<td>.008</td>
</tr>
<tr>
<td>Cardiac</td>
<td>17.5% (35)</td>
<td>18.1% (18)</td>
<td>17% (17)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Fistula</td>
<td>5.5% (11)</td>
<td>5% (5)</td>
<td>5.9% (6)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>11.5% (23)</td>
<td>15.1% (15)</td>
<td>7.9% (8)</td>
<td>.06</td>
</tr>
</tbody>
</table>
Respiratory complications were more frequent in group B than in group A (19 cases, 19.2%, vs 7 cases, 6.8%, P = .008).

**Predictors of Pulmonary Complications**

Univariate logistic regression showed that pulmonary complications were more frequent (1) in patients over the age of 70 years as compared with those aged 70 or less (25.7% vs 10.2, P = .02), (2) in those with a lower Dlco/VA% (18.3% vs 5.95%, P = .06), and (3) in patients who received preoperative chemotherapy (19.2% vs 6.8%, P = .008). Respiratory complications after right pneumonectomy were more frequent (15.6%) than after left pneumonectomy (10.3%), but the difference was not significant (P = .2). Patients with previous cardiac problems had a higher rate of respiratory complications (18.9%) than did patients with no previous cardiac events (10.4%), but the difference was not significant (P = .10).

Logistic regression confirmed the role of age (P = .0017, OR = 6.3), preoperative chemotherapy (P = .0146, OR = 4.4), and Dlco/VA% (P = .0515, OR = 0.33) as risk factors causing respiratory complications (Table 3). No risk factor was identified by logistic regression for nonrespiratory complications.

**Discussion**

Some data exist in the scientific literature on the theoretical increased risk of respiratory complications after induction chemotherapy. This problem becomes crucial in patients who undergo pneumonectomy in which any event impairing pulmonary function could be fatal.

The first result from our analysis was that, after pneumonectomy, respiratory complications are 3 times more frequent in patients who received induction chemotherapy than in those who did not. The supposed mechanism is a temporary decrease in the diffusion capacity of the alveolar-capillary membrane, usually in the order of 15% but sometimes as high as 40% to 50%. This impairment probably amplifies the damage to the membrane caused by inflammatory or infective agents facilitating intra-alveolar exudates.

The best functional parameter to assess membrane impairment is Dlco, which has been demonstrated to be a useful independent parameter in preoperative functional evaluation of patients undergoing lung resection. Inasmuch as Dlco is strictly linked to lung volumes, which are modified to a variable extent in the majority of patients after chemotherapy, Dlco/VA is probably a more reliable indicator of membrane alteration after chemotherapy. Direct data on Dlco/VA loss after chemotherapy were unfortunately not available in our study, because only patients who underwent mediastinoscopy at our institution before induction treatment had Dlco assessment both before and after chemotherapy. However, patients who received preoperative chemotherapy had a lower Dlco/VA than did those who did not receive induction treatment, and Dlco/VA was confirmed as a risk factor for respiratory complications. The practical consequence is that it is worthwhile to study diffusion capacity (including Dlco/VA) both before and after chemotherapy to identify patients with a marked impairment, who could represent a high-risk group for postoperative respiratory complications.

Apart from preoperative chemotherapy and Dlco/VA, advanced age was confirmed as an independent predictor of respiratory complication. In fact, it has long been established that patients older than 70 years have a higher postoperative mortality rate than do younger patients. These data were confirmed by our series, in which patients over 70 years of age represented 17% of the population and had a postoperative mortality of 11.4% (4/35).

Surprisingly, the increased risk for respiratory complications did not affect overall postoperative mortality, even considering 90-day deaths. The reason is probably due to the fact that chronic respiratory failure was inserted as a postoperative respiratory complication, whose impact on life expectancy should be evaluated after a longer period than the first 3 months after surgery.

Right pneumonectomy, even after induction chemotherapy, did not show a catastrophic impact on morbidity in our series (overall mortality 6.2%). This was in contrast to the series described by Martin and associates, who reported a 25% mortality in patients undergoing right pneumonectomy after induction treatment, raising questions about the usefulness of such a procedure in patients with N2 disease. This difference is probably due to several factors: we did not include extended resections, which are most often rightsided procedures having a higher mortality; moreover, we excluded preoperative radiotherapy, whereas in Martin’s series 18% of patients received induction chemoradiotherapy. Both considerations could explain why the postpneumonectomy ARDS rate from the same institution remains high.

During the considered period, the rate of rethoracotomy for hemostasis was high (11%). Our policy of reoperation in

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**Table 3. Logistic regression considering preoperative chemotherapy, age (>70 vs ≤ 70 years), and Dlco/VA% (> vs <88.5%, representing the median of the population) confirmed the role of these three factors**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>χ²</th>
<th>Point estimate</th>
<th>CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>−2.95</td>
<td>0.613</td>
<td>&lt;0.001</td>
<td>1.34-14.5</td>
<td>2-20.1</td>
</tr>
<tr>
<td>Preop chemo</td>
<td>1.48</td>
<td>0.608</td>
<td>0.014</td>
<td>4.419</td>
<td>1.34-14.5</td>
</tr>
<tr>
<td>Age</td>
<td>1.84</td>
<td>0.589</td>
<td>0.001</td>
<td>6.354</td>
<td>2-20.1</td>
</tr>
<tr>
<td>Dlco/VA%</td>
<td>−1.10</td>
<td>0.568</td>
<td>0.051</td>
<td>0.331</td>
<td>0.1-1.007</td>
</tr>
</tbody>
</table>

SE, Standard error; CL, confidence limits; Dlco/VA, diffusion capacity for carbon monoxide adjusted for alveolar volume.
cases of radiologic evidence of intrathoracic clouting and mild progressive anemia, even in the absence of hemodynamic instability, explains the 7% reoperation rate in patients not receiving preoperative chemotherapy. In patients undergoing chemotherapy, the incidence of rethoracotomy was twice that rate. The reason remains unclear, considering that coagulation status was checked in all cases the day before surgery and that surgery was postponed until it was normal.

The supposed mechanism, postulated from liver surgery, is a transient reduction in hepatic function caused by chemotherapy. This effect, associated with higher blood loss resulting from extensive mediastinal nodal dissection and the azygos vein section that we routinely perform on the right side after chemotherapy (with a possible consequent increased venous pressure on chest wall vessels), may justify the increased risk of bleeding in chemotherapy patients.

As expected, the stage distribution between groups was not homogeneous, because preoperative chemotherapy was administered to patients having a more advanced disease. Certainly, from a speculative point of view, we can only confirm that these two factors (chemotherapy and stage) are linked to a higher risk of respiratory complications, but the weight of both factors was not evaluated. We did not attempt to adjust data by stage for several reasons. First, a detrimental effect on respiratory function has been demonstrated for chemotherapy but not for stage alone. Moreover, stage did not affect the type of operation that patients received, since in all cases a standard pneumonectomy was performed. Finally, even admitting a hypothetical peculiar effect of stage per se, this would not change our evidence-based

policy of offering induction chemotherapy to patients with advanced-stage lung cancer.

In conclusion, results from our series have demonstrated that standard pneumonectomy is a safe procedure with a mortality rate lower than 5%, which increases in patients over the age of 70 years. In case of induction chemotherapy, mortality remains under 5% but the risk of respiratory complications is significantly increased. In candidates for pneumonectomy after induction treatment, a complete respiratory assessment, mainly focused on lung diffusion, should be performed before and after chemotherapy to predict postoperative risk.

References