Morbidity after surgery for non-small cell lung carcinoma is not related to neoadjuvant chemotherapy

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Abstract

Objectives: To compare postoperative morbidity and mortality rates in two groups of operated non-small cell lung carcinoma patients (NSCLC) with or without induction chemotherapy. Methods: This is a case–control study on 42 cases and 42 controls. Cases (Group A) underwent induction chemotherapy. Chemotherapy indications and regimens were variable. Control cases (Group B) were randomly selected among 494 NSCLC comparable patients operated on in the same period of time. The selection criteria for operation were the same in both groups. Dependent outcomes were operative death and complications. Independent selected variables were: age, co-morbidity, predicted postoperative FEV1% (1 s forced expiratory volume in percentage), type of surgery and clinical and pathological staging. All postoperative events and independent variables were prospectively registered. Chi-square and risk calculations on contingency tables and one-way ANOVA have been tested. Results: Both series are comparable in demographics, preoperative variables and type of surgery. No mortality has been registered. In Group A, the overall morbidity was 26.2% (11 out of 42 cases), and in Group B, this was 42.9% (18 out of 42 cases; \( P = 0.084 \)). Morbidity was not related to the type of surgery (pneumonectomy vs. other; \( P = 0.205 \) in Group A and \( P = 0.08 \) in Group B). Pathological staging did not influence the postoperative outcome, either in Group A (\( P = 0.72 \); odds ratio, 1.515; 95% confidence interval (CI), 0.375–6.122) or Group B (\( P = 0.299 \); odds ratio, 0.4; 95% CI, 0.089–1.797). Conclusions: Induction chemotherapy in NSCLC has no influence on postoperative morbidity. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Non-small cell lung carcinoma; Neoadjuvant chemotherapy; Morbidity

1. Introduction

Surgical resection is the best therapy for localized non-small cell lung carcinoma (NSCLC). Unfortunately, only around 30% of cases have resectable disease at diagnosis [1]. Although complete resection for clinical stage IIIA disease can be feasible, the results are discouraging [2], with most patients dying early due to local relapse or distant metastases [3]. A few randomized prospective clinical trials have been carried out to try and demonstrate that preoperative chemotherapy increases survival in this subset of patients [4,5].

The influence of induction chemotherapy on the postoperative outcome remains controversial. While some authors consider chemotherapy to be a risk factor [6–8], this is not the case for others [9,10].

The aim of this study was to compare morbidity and mortality rates in two groups of operated patients with or without induction chemotherapy. To evaluate the indications or the influence of neoadjuvant chemotherapy on long-term survival is beyond the scope of this report.

2. Methods

We have designed a case–control study on two groups of patients. Group A cases were referred to us for surgical resection following preoperative chemotherapy without radiotherapy from March 1994 to December 2000. The treatment indications and protocols were decided by the referring physicians. Surgery was recommended if no tumour progression was demonstrated by computed axial tomography (CT) during treatment. Control cases (group B) were randomly selected among 494 NSCLC patients operated on by us in the same period of time, in whom no preoperative chemotherapy was indicated. Coincidence in the year of surgery, age of the patient (same decade of life) and type of operation were required to enter the control group. The postoperative outcome was blinded at the time of selection. Final assignment to the control group was performed by a computer-aided randomized number series.

The selection criteria for operation were the same in the
two groups and consisted of: Karnofski index over 50%, a predicted postoperative 1 s forced expiratory volume in percentage (ppoFEV1%) [11] of over 30%, absence of hypercarbia and no concomitant bad prognostic systemic disease.

Neoadjuvant treatment consisted of three or four cycles including paclitaxel and carboplatin in most cases (Table 1).

For clinical staging, a thoraco-abdominal CT scan was indicated in all cases; 17 cases (all positive) and ten controls (all negative) underwent mediastinoscopy. In all patients, a mediastinal lymphadenectomy was performed. The samples were evaluated by the same pathologist by hematoxylin–eosin staining and optical study, and tumour extension was classified according to 1977 UICC–AJCC [2]. Thereafter, the patients were grouped into localized (stages IA–IIB) and extended (stages IIIA–IV) according to the extent of the disease.

The analyzed dependent outcomes were the occurrence of postoperative death (in-hospital or 30 days after discharge) and complications. Considered complications were technical (wound infection or dehiscence, air-leak over 5 days, haemothorax, pleural empyema, chylothorax and broncho-pulmonary (wound infection or dehiscence, air-leak over 5 days, and complications. Considered complications were technical (wound infection or dehiscence, air-leak over 5 days, haemothorax, pleural empyema, chylothorax and broncho-pulmonary fistula), cardiac (congestive failure, non-preexisting arrhythmia, angina, infarct and pulmonary oedema); pulmonary (pneumonia, atelectasis, need of mechanical ventilation after extubation at the operating theatre, hypercarbia and PO$_2$ of under 60 mmHg at discharge), vascular (deep vein thrombosis, pulmonary embolism) and others (urine infection or abdominal events).

Independent variables analyzed were: age, sex, preoperative co-morbidity (cardiac rhythm disturbances, ischaemia, valvular disease, diabetes mellitus), ppoFEV1%, clinical and surgical-pathological staging and type of surgery (exploratory, lobectomy, lobectomy and bronchoplasty, pneumonectomy and sleeve pneumonectomy). To increase the power of the analysis, the variable ‘type of surgery’ was converted to a binary one: pneumonectomy or other.

Both independent variables and postoperative events were prospectively recorded and stored in a computed database.

The dependence of nominal variables was tested by the Chi-square test and risk calculation on contingence tables. Differences between means for continuous variables were evaluated by one-way ANOVA analysis. All calculations were performed by SPSS 9.0 for Windows.

### 3. Results

Forty-two of 49 referred post-chemotherapy cases have been included in the study. Six patients were judged to be inoperable because of bad performance status (three cases) or low ppoFEV1% (three cases). One additional case diagnosed with two bilateral simultaneous NSCLCs has been excluded from the analysis; hence, 42 control cases have been selected.

The demographic characteristics are presented in Table 2. The mean ages of both groups (Group A, 58.6 years; Group B, 60.8 years; $P = 0.339$) were similar, as well as the ppoFEV1% means (Group A, 60.9%; Group B, 64.5%; $P = 0.38$).

In the control group, the percentages of cases having cardiac co-morbidity (14.3%) or diabetes mellitus (14.3%) were slightly higher than those in Group A (9.5 and 4.8%; $P = 0.738$ and $P = 0.265$, respectively).

The clinical and pathological tumour extensions are presented in Table 3. Downstaging was achieved in 50% of clinical extended tumours (16 out of 32).

The resectability rate in Group A was 95.2% (40 cases).

### Table 2
Demographics and preoperative data

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male; %)</td>
<td>92.9</td>
<td>90.5</td>
<td>1</td>
</tr>
<tr>
<td>Age$^a$</td>
<td>58.6 ± 11.4 (35–74.1)</td>
<td>60.8 ± 10.3 (40–77)</td>
<td>0.339</td>
</tr>
<tr>
<td>ppoFEV1%$^a$</td>
<td>60.9 ± 16.3 (33.5–96.6)</td>
<td>64.5 ± 19.2 (36.3–111.1)</td>
<td>0.38</td>
</tr>
<tr>
<td>Cardiac co-morbidity (%)</td>
<td>9.5</td>
<td>14.3</td>
<td>0.738</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>4.8</td>
<td>14.3</td>
<td>0.265</td>
</tr>
</tbody>
</table>

$^a$ Mean ± SD (rank).

### Table 1
Chemotherapy regimens in Group A patients

<table>
<thead>
<tr>
<th>Patients (n; %)</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin–Paclitaxel</td>
<td>21 (50)</td>
<td></td>
</tr>
<tr>
<td>Carboplatin–Paclitaxel (six cycles)</td>
<td>2 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Carboplatin–VP16</td>
<td>3 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Cisplatin–Gemcitabine</td>
<td>7 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Cisplatin–Mitomycin–Hosfamide</td>
<td>3 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Cisplatin–Paclitaxel–Gemcitabine</td>
<td>7 (16.7)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Unless indicated otherwise, 3–4 cycles.

### Table 3
Comparison between clinical and pathological staging in both groups

<table>
<thead>
<tr>
<th>Tumour extension</th>
<th>Group A (n; %)</th>
<th>Group B (n; %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA–IIB</td>
<td>10 (23.8)</td>
<td>42 (100)</td>
</tr>
<tr>
<td>IIA–IV</td>
<td>32 (74.2)</td>
<td>0</td>
</tr>
<tr>
<td>Pathological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA–IIB</td>
<td>26 (61.9)</td>
<td>31 (73.8)</td>
</tr>
<tr>
<td>IIA–IV</td>
<td>16 (38.1)</td>
<td>11 (26.2)</td>
</tr>
</tbody>
</table>
In 20 cases, lobectomies were performed (two bronchoplasticies), and pneumonectomies in another 20 cases (four sleeve tracheoplasties). No mortality was registered in any group.

The overall morbidity in Group A was 26.2%, and 42.9% in Group B (P = 0.084). Five cases (11.9%) and five controls had technical complications. Six cases (14.3%) and 13 controls (30.9%) suffered other kinds of postoperative problems (P = 0.069; Table 4). In Group A (Table 5), six cases in pathological stages IA–IIB and five in pathological stages IIA–IIV suffered complications (P = 0.72; odds ratio, 1.5; 95% confidence interval (CI), 0.4–6.1). These data are not different from those recorded in Group B (15 complicated cases in localized and three in extended disease: P = 0.299; odds ratio, 0.4; 95% CI, 0.1–1.8).

Pneumonectomy was not associated with higher morbidity (P = 0.539). Table 6 depicts complications depending on the type of surgery.

4. Discussion

The aim of this study was to compare the postoperative morbidity and mortality in two series of operated NSCLC cases to evaluate if preoperative chemotherapy can be considered as a risk factor. We have presented a small series of cases (only 42 patients in 6 years), probably reflecting that induction chemotherapy is not considered as a routine protocol for advanced non-small cell lung cancer in some centres.

The efficacy of neoadjuvant chemotherapy is still controversal, as well as the indications and patient selection criteria. Induction treatment for clinical stages under IIMA is currently under investigation [12]. Although discussion of this topic is beyond the scope of this publication [13,14], we think that such a therapy in localized tumours should be considered only in a randomized, controlled study.

Our current clinical staging protocol does not include routine mediastinoscopy as has been advocated by some authors [15]. Findings at pre-treatment mediastinoscopy have been reported to be the most important prognostic factors for long-term survival [16].

As we have stated before, we have not been involved in the clinical staging of most patients; hence the low numbers of invasive staging procedures performed and the relatively high percentage of cases clinically classified as IA–IIB.

In this report, we have controlled some previously published risk factors, such as the age of the patient [17], co-morbidity [18], type of operation [19], and predicted postoperative function [20]. The selection criteria for the control group (similar age and operability criteria of the patients, same year of operation and similar type of surgery) render both series comparable.

We have not controlled preoperative nutritional status, because of the absence of prospective data. Since this is a variable with possible influence on the postoperative evolution [21], it can be considered as a limitation of the study.

Preoperative chemotherapy has been recognized as a risk factor by some authors. In several reports, patients underwent induction chemotherapy and radiotherapy [6,8,22,23]. The published mortality in these series ranked between 3.8 and 12% and is mainly related to pneumonectomy [6,22]. This information has not been confirmed in recent publications [10,24]. The association of radiotherapy [25], or, according to Friedel et al. [14], high radiation dose could be related to most of the postoperative morbidity.

Chemotherapy alone has been previously evaluated as a risk factor [7,10] and the results are controversial. In some reported series, the number of treated cases is small [9]. Bernard et al. [7] concluded that chemotherapy increases the risk of postoperative morbidity, although in their series, the odds ratio for this variable was 0.48 (95% CI, 0.25–0.93). In fact, in the cited report, the rate of postoperative complications in patients with chemotherapy was lower, but not statistically significant, as we have found in our experience.

Even though, in our series, the selection criteria for thoracotomy were the same in both cases and controls, a bias in
patient selection can be suspected. The mean age, as well as the mean ppFEV1%, are lower in Group A, and the rate of patients suffering co-morbidity is higher in Group B. Although the figures do not reach statistical significance, the data suggest that some high-risk cases are not referred for surgery after chemotherapy. In our team, surgical cases are usually randomly assigned to surgeons. Nevertheless, we accept that a bias due to surgical expertise could have played a role in the results.

Recently, Sieghenthaler et al. [10] published that preoperative chemotherapy does not increase the surgical morbidity in NSCLC. In their experience, almost half of the patients (36 out of 76) were not included in any protocol setting and were treated with variable chemotherapy regimens. The high variability of induction treatments reported by these authors and described in our series, should be considered as a limiting factor in order to draw valuable conclusions.

Keeping in mind the aforementioned limitations of the study, it can be concluded that induction chemotherapy can not be considered as a risk factor for postoperative morbidity.

References

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