Does induction treatment increase the risk of morbidity and mortality after pneumonectomy? A multicentre case-matched analysis

Majed Refai a,*, Alessandro Brunelli a, Gaetano Rocco b, Mark K. Ferguson c, Sergio N. Fortiparri d, Michele Salati a, Antonello La Rocca b, Kenji Kawamukai d

a Umberto I Regional Hospital Ancona, Ancona, Italy
b National Cancer Institute Pascale Foundation, Naples, Italy
c The University of Chicago, USA
d Bellaria-Maggiore Hospital, Bologna, Italy

Received 8 June 2009; received in revised form 9 September 2009; accepted 13 September 2009

Abstract

Background: The objective of this investigation was to compare postoperative morbidity and early and late mortality in patients after pneumonectomy for non-small-cell lung cancer (NSCLC) with or without induction neo-adjuvant therapy. Methods: This is an observational study performed on prospectively collected data at four tertiary referral centres (2000—2007). Of 225 pneumonectomies for NSCLC, 81 patients underwent neo-adjuvant chemotherapy. Several perioperative variables were used in identifying propensity score-matched pairs of patients with and without induction treatment. The matched groups were then compared in terms of morbidity, early (30-day or in-hospital) and 90-day mortality. Results: The overall cardiopulmonary morbidity, early mortality and 90-day mortality rates were 30% (67 patients), 7.1% (16 patients) and 9.8% (22 patients), respectively. Propensity score analysis yielded 56 well-matched pairs of patients with and without induction chemotherapy. The two groups had similar early and late mortality rates: four versus four (p = 1) and seven versus seven (p = 1), respectively. Moreover, the incidence of cardiopulmonary morbidity and bronchopleural fistula were also similar in both the groups: 19 versus 17 patients (Fisher’s exact test p = 0.7) and two versus three patients (Fisher’s exact test, p = 0.7), respectively. Twenty-one patients with induction chemoradiotherapy were analysed separately and compared with well-matched counterparts without any induction treatment. No significant differences were identified in terms of early mortality (1 vs 0, p = 1), 90-day mortality (1 vs 0, p = 1), cardiopulmonary complications (5 vs 5, p = 1) and bronchopleural fistula (1 vs 1, p = 1). Conclusions: Current regimens of induction treatment do not seem to increase the risk of morbidity, early mortality and late mortality after pneumonectomy in properly selected patients. This study warrants confirmation from future multicentre prospective randomised trials powered on early outcomes.

© 2009 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.

Keywords: Lung cancer; Pulmonary resection; Induction chemotherapy; Radiotherapy; Morbidity; Mortality

1. Introduction

Advances in perioperative management and surgical techniques have contributed to improved outcomes after pulmonary resection. Yet, pneumonectomy remains associated with high complication and mortality rates [1—4], and the influence of induction treatment on its early outcomes is still undefined and debatable [5]. This issue has been investigated in the previous studies with conflicting results [6—10]. Majority of these studies were retrospective, based on old series, and none of the observational analyses used a case-matching technique for adequate balanced comparison.

We designed this study to compare postoperative morbidity, early (30-day or in-hospital) and 90-day mortality rates in propensity score case-matched patients who underwent pneumonectomy for non-small-cell lung cancer (NSCLC) with or without induction therapy.

2. Patients and methods

This is an observational study performed on prospectively collected data at four tertiary referral centres (2000—2007). We analysed 225 patients (185 males and 40 females) undergoing pneumonectomy for NSCLC. Pneumonectomies for secondary malignant disease or non-neoplastic diseases were excluded. Eighty-one patients underwent neo-adjuvant chemotherapy and 21 induction chemo-radiotherapy. Data collection in each centre was approved by the local Institutional Review Board after informed consent was obtained.

* Corresponding author. Address: Via San Vincenzo 5/f Polverigi, Ancona, Italy. Tel.: +39 07159634439; fax: +39 0715964481.
E-mail address: majedit@yahoo.com (M. Refai).
Criteria for resectability were assessed by computed tomography (CT) scan, bronchoscopy and, whenever indicated, mediastinal staging procedures (cervical mediastinoscopy, fine-needle aspiration through bronchoscopy or video-assisted thoracoscopy). Operability was evaluated by pulmonary function tests, extensive cardiologic evaluation and exercise testing. Patients with a predicted postoperative forced expiratory volume in 1 s (FEV₁) and predicted postoperative carbon monoxide diffusion lung capacity (DLCO) less than 30% in association with a poor exercise tolerance (maximum oxygen consumption (VO₂max) less than 10 ml kg⁻¹ min⁻¹) were deemed inoperable, according to the published guidelines [11].

As a rule, surgery was performed through a muscle-sparing thoracotomy by qualified thoracic surgeons. In most patients, the main bronchus was divided and closed using mechanical staples and, in all patients submitted to induction treatment, the bronchial stump was buttressed with viable tissue (intercostal muscle flap or pericardial fat pad). Patients were extubated in the recovery room and initially monitored in intensive care or high-dependency units (according to the hospital structural and organisational characteristics), and then transferred to a dedicated thoracic ward whenever deemed in stable cardiorespiratory condition. Postoperative treatment was standardised in each centre and focussed on thoracotomy wound pain control, chest physiotherapy, early mobilisation and antithrombotic and antibiotic prophylaxis.

2.1. Statistical analysis

Definition of variables and outcomes were standardised across centres. Each centre appointed a data manager who was responsible for the accuracy and completeness of data. Data were collected at individual centres and submitted to a centralised data system. Incomplete or inconsistent data, if any, were returned to individual centres for revision before being used for analysis.

To minimise selection bias and the influence of several clinical confounders on outcomes, propensity score methodology was used to match patients submitted to induction treatment with counterparts without induction treatment [12,13]. The aim of the analysis was to match patients with and without neo-adjuvant chemotherapy according to the baseline characteristics and compare the outcomes (i.e., morbidity, 30-day/in-hospital mortality and 90-day mortality) between the matched groups. The conditional probability to be treated (propensity score) was estimated by logistic regression analysis incorporating the following variables: age, gender, diabetes, DLCO, FEV₁, predicted postoperative DLCO (ppoDLCO), predicted postoperative FEV₁ (ppoFEV₁), presence of coronary artery disease and side (right or left) of pneumonectomy. As stated by its developers [14], the propensity model is not parsimonious. In fact, the goal is to balance patient characteristics by incorporating ‘everything’ recorded that may relate to either systematic bias or simply bad luck that has otherwise unbalanced the comparison groups of interest, ignoring usual concerns about model overdetermination [13]. All variables were at least 95% complete, and sporadic missing values were imputed by taking the most frequent response category or averaging non-missing values for continuous variables. Greedy matching techniques were then used to select patients who underwent induction treatment with counterparts without induction treatment by choosing the patient with the nearest propensity score [13]. The procedure yielded 56 well-matched pairs with and without neo-adjuvant chemotherapy.

The same procedure was repeated for matching pairs of patients with induction radio-chemotherapy and with surgery alone. Normality of distribution of numeric variables was assessed by the Shapiro Wilk’s test. Continuous variables of the two groups of propensity score-matched patients were compared by the Wilcoxon rank test (non-parametric distribution) or by the Student’s t-test (normal distribution). Categorical variables were compared by the chi-square or the Fisher’s exact tests as appropriate.

All the statistical tests were two-tailed, with a significance level of p = 0.05, and were performed on the statistical software Stata 8.2 (Stata Corp, College Station, TX, USA).

3. Results

The characteristics of patients enrolled in this study are shown in Table 1. Total cardiopulmonary morbidity, inhospital/30-day mortality, 90-day mortality and 6 months mortality rates were 30% (67 patients), 7% (16 patients), 10% (22 patients) and 13% (29 patients), respectively.

Propensity score case matching was performed to select two matched samples of patients (with and without induction chemotherapy) for balanced comparative analysis. After excluding those cases undergoing radiotherapy alone or in combination with chemotherapy, propensity score case matching yielded 56 well-matched pairs of patients (with and without chemotherapy) (Table 2).

We were not able to detect any differences of outcomes between the two matched groups (Table 3). Early, 90-day and 6-month mortality rates did not differ between the two matched groups (Fisher’s exact test): four versus four (p = 1),

Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>n/a 12</th>
<th>N1 11</th>
<th>N2 09</th>
<th>N7 25</th>
<th>N8 17</th>
<th>N9 25</th>
<th>N10 12</th>
<th>N11 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.9 (8.9)</td>
<td>185 (82%)</td>
<td>17 (8%)</td>
<td>83 (37%)</td>
<td>82.0 (16.6)</td>
<td>75.8 (19.5)</td>
<td>50.0 (12.2)</td>
<td>46.8 (13.2)</td>
</tr>
<tr>
<td>Male gender (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁, % (mean, SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLCO % (mean, SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ppoDLCO % (mean, SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right side (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT stage (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN stage (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction chemotherapy (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction chemo-radiotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
All variables were found not significantly different (p = 0.05) between the matched groups.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Neo-adjuvant chemo-radiotherapy (56 pairs)</th>
<th>Surgery alone (56 pairs)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality (n)</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>90-day mortality (n)</td>
<td>7</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>6-month mortality (n)</td>
<td>8</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Cardiopulmonary morbidity (n)</td>
<td>19</td>
<td>17</td>
<td>0.7</td>
</tr>
<tr>
<td>Bronchopleural fistula (n)</td>
<td>2</td>
<td>3</td>
<td>0.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Neo-adjuvant chemo-radiotherapy (21 pairs)</th>
<th>Surgery alone (21 pairs)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality (n)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>90-day mortality (n)</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>6-month mortality (n)</td>
<td>3</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Cardiopulmonary morbidity (n)</td>
<td>5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Bronchopleural fistula (n)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Cardiac co-morbidity defined as presence of coronary artery disease, any previous cardiac surgery, current treatment of cardiac failure, arrhythmia or hypertension. All variables were found not significantly different (p > 0.05) between the matched groups.

Table 4
Case-matched comparison of outcomes (21 pairs): neo-adjuvant chemotherapy patients versus surgery alone patients.

Table 2
Characteristics of the propensity score case-matched groups used for comparison (neo-adjuvant chemotherapy versus surgery alone, 56 pairs; neo-adjuvant chemoradiotherapy versus surgery alone, 21 pairs).

Table 3
Case-matched comparison of outcomes (56 pairs): neo-adjuvant chemotherapy patients versus surgery alone patients.

seven versus seven (p = 1) and eight versus eight patients (p = 1), respectively. Similarly, the incidence of cardiopulmonary morbidity and bronchopleural fistula was similar: 19 versus 17 (p = 0.7) and two versus three cases (p = 0.7), respectively.

Case-matched comparison of patients undergoing induction chemo-radiotherapy with those without any form of induction treatment (21 pairs; Table 2) did not reveal any significant differences in early mortality (1 vs 0, p = 1), 90-day mortality (1 vs 0, p = 1), 6-month mortality (3 vs 0, p = 0.2), cardiopulmonary complications (5 vs 5, p = 1) and bronchopleural fistula (1 vs 1, p = 1) (Table 4).

4. Discussion

The results of surgical resection alone for regionally advanced NSCLC (stages II–III) are poor. Most patients die of locally recurrent or distant metastatic disease; hence, there is great interest in the application of chemotherapy and/or radiotherapy in the induction settings. The present study was performed on a contemporary dataset and showed that induction treatment did not appear to increase the risks of morbidity, early mortality and late mortality after pneumonectomy in properly selected patients.

To our knowledge, there are only two randomised trials comparing the outcome of pneumonectomy patients with and without chemotherapy [6, 15]. Both of these studies did not find an increase in mortality rates after induction treatment. Nevertheless, none of these studies was specifically designed and powered to assess early outcomes, but rather focussed on long-term survival. Other retrospective studies showed conflicting results [4], and were mostly based on old series with different chemotherapy agents and without proper matched controls selected by balancing scores.

Our study, although retrospective, may be a useful addition to the current literature using balancing scores technique to match pairs of patients. Several studies in the past have shown an association between induction treatment and an increased risk of bronchopleural fistula after pneumonectomy [16, 17]. We were not able to demonstrate an increase in this complication. The use of modern regimens of chemotherapeutic agents, better patient selection and, most of all, the use of viable buttressing tissue to cover the bronchial stump in all patients undergoing induction treatment may explain this favourable finding.

It is incumbent on thoracic surgeons to be critically aware of the strengths and weaknesses of various trials that advocate or criticise the use of adjuvant or induction therapy and the surgical approach to adopt. The construction of prospective randomised trials bears important clinical and ethical issues [18]. In this regard, propensity score case-matched analysis [12, 13] is considered the most rigorous method available for the so-called ‘apples-to-apples’ investigation of causal effects on outcomes in a non-randomised setting [19]. Because associations found through traditional multivariable regression may be misleading, because one covariate of interest may be underrepresented within levels of another, propensity scores are recommended to adjust for confounding background characteristics [19]. For this reason, propensity score case matching was performed in our observational study to select two matched samples of patients (with and without induction chemotherapy) for balanced comparative analysis.

Despite the recommendations of the American College of Chest Physicians (ACCP) [20] to avoid performing pneumonectomy after induction chemo-radiotherapy, we found that
case-matched comparison of patients undergoing induction chemo-radiotherapy with those without any form of induction treatment did not reveal any significant differences in terms of morbidity, early mortality and late mortality. These results must be interpreted with caution; we believe that every attempt must be made to avoid pneumonectomy by performing sleeve lobectomy when feasible [21,22]. However, pneumonectomy after induction treatment may be performed when it is needed, but should be limited to dedicated general thoracic surgery departments.

Our study has potential limitations. It is not a randomised trial. Knowing that the propensity score analysis remains the most rigorous method for investigating causal effects, it cannot completely account for unknown variables affecting the outcome that are not correlated strongly with the measured variables. In addition, our study was an observational study performed at four different centres, with patients treated with different platinum-based chemotherapy or radiotherapy induction protocols/schedules, and detailed information about patients’ compliance were not available.

In conclusion, our study showed that induction treatment did not increase the risk of morbidity, early mortality and late mortality after pneumonectomy in properly selected patients operated on in dedicated general thoracic surgery departments. Future multicentre prospective randomised trials adequately powered on early outcomes are warranted to confirm these results.

References


Appendix A. Conference discussion

Dr A. Turna (Istanbul, Turkey): Did you apply any selection criteria for the patients who required pneumonectomy after induction therapy? You declared that it can be done in selected patients, but did you apply any special criteria for the patients who required pneumonectomy?

Dr Refai: I didn’t understand your question.

Dr Turna: For example, in a 70-year-old patient who required pneumonectomy after induction therapy, did you perform pneumonectomy?

Dr Refai: The preoperative evaluation was done based on the ACCP guidelines for selecting patients.

Dr Turna: So you did not exclude any patients besides these criteria?

Dr Refai: No.

Dr J. Schirren (Wiesbaden, Germany): How many pneumonectomies did you do on the right side and how high were the doses from the radiation and did you cover the bronchial stump with tissue?

Dr Refai: We did 106 pneumonectomies on the right side, and the bronchial stump was always covered with viable tissue for example with intercostal muscle or pericardial fat.

Dr H-B. Ris (Lausanne, Switzerland): You had in fact a difference in postoperative morbidity and mortality which was higher after radiotherapy. The difference was, however, not statistically significant but this might be related to the small sample size of your collective. Is it correct that you had a three times higher mortality rate after induction radiotherapy and pneumonectomy compared to induction treatments without irradiation?

Dr Refai: You are right. The number is small. So we agree that the lack of statistical difference may be due to small sample size.
Dr Ris: There is a problem with the interpretation of your data. You cannot say that you had no difference if you have a three times higher mortality rate in one group just because the sample size is too small to reach statistical significance.

Dr Refai: Indeed we didn’t say that there is not difference, we said that we didn’t have a statistically significant increase in mortality.

Dr N. Altorki (New York, NY): I congratulate you on using the propensity scoring, but propensity scoring does not eliminate the need for appropriate sample sizes to compare. Most of the papers coming from the cooperative groups show that post-pneumonectomy early mortality is higher after chemotherapy and radiation.

These operations should be done in very specialised centres where mortality was shown to be lower.

Do you know how much radiation was delivered in your 21 patients?

Dr Altorki: But that would be important information if you want to add to your manuscript.

Dr Refai: We agree.

Dr F. Detterbeck (New Haven, CT): Did your propensity matching also match right versus left pneumonectomy or did you do a separate analysis to see if there was a difference between right and left?

Dr Refai: We included the side of resection in the construction of propensity score. In a separate subgroup analysis we were not able to find any difference in outcome related to the side of pneumonectomy.