Effect of bilateral mediastinal lymphadenectomy on short-term pulmonary function

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Abstract

Objective: To assess if the bilateral mediastinal lymphadenectomy results in lymphatic congestion in the lungs producing clinically significant impairment of respiratory function. Methods: In the prospective, randomized, double-blind clinical study, non-small cell lung carcinoma patients underwent preoperatively mediastinoscopy or the transcervical extended mediastinal lymphadenectomy (TEMLA). In both groups, the blood gas analysis and spirometry were measured preoperatively and on the 1st, 3rd, and 5th postoperative day, and the carbon monoxide diffusing capacity of the lung (DLCO) and lung compliance were measured preoperatively and on the 3—5 postoperative day. Any respiratory complications were also recorded. Results: Forty-one patients were randomized: 21 to the TEMLA group and 20 to the mediastinoscopy group. There was no significant difference of the baseline and the 1st, 3rd, and 5th day measurements of vital capacity and forced expiratory volume (FEV1) (p > 0.98), pH, pO2, pCO2, standard bicarbonates and base excess (p > 0.31), nor significant difference of baseline and 3—5 day measurements for DLCO (p = 0.91) and lung compliance (p = 0.38). The incidence of respiratory insufficiency was not significantly different (p = 0.51). Conclusions: (1) Complete excision of mediastinal lymph nodes stations 1, 2R, 2L, 3A, 4R, 4L, 5, 6, 7, and 8 (TEMLA) is not associated with greater incidence of respiratory insufficiency comparing with standard mediastinoscopy. (2) The TEMLA procedure does not produce greater alterations in spirometry, blood gas analysis, DLCO and lung compliance comparing with standard mediastinoscopy.

Keywords: Lymph node excision; Mediastinoscopy; Non-small cell lung carcinoma; Diffusing capacity; Lung compliance; Blood gas analysis

1. Introduction

Complete, bilateral dissection and pathological assessment of all lymph nodes from each mediastinal station is an ideal model of pretreatment surgical staging in non-small cell lung carcinoma (NSCLC) patients. Although no such method is currently available, the recently developed technique of transcervical extended mediastinal lymphadenectomy (TEMLA) is close to this paradigm. It has been proved to be safe and highly effective in mediastinal staging [1], but the relatively high number of patients found thereafter unfit for the definite surgery has risen doubts regarding the potential functional respiratory impairment due to the extensive mediastinal dissection and lymphatic congestion in the lungs. To elucidate this problem, we have incorporated the investigation of the effect of bilateral mediastinal lymphadenectomy on pulmonary function into a larger randomized controlled study comparing the diagnostic yield of the TEMLA with standard cervical mediastinoscopy.

2. Materials and methods

The study was approved by the Institutional Review Committee and the Bioethical Committee of the Jagiellonian University in Cracow. All the patients received detailed information regarding the procedures and their potential risk and benefits were discussed. The informed consent was obtained from all the patients.

2.1. Clinical questions

(1) Does the TEMLA produce more pronounced impairment of respiratory function than standard cervical mediastinoscopy?
(2) Is TEMPLA associated with greater risk of respiratory complications, as compared with mediastinoscopy?

2.2. Design

Prospective, randomized, double-blind clinical study. Patients and the staff members assessing and recording the end-points did not know the allocation. The blinding was possible by using for mediastinoscopy longer, 6 cm incision, the same as for the TEMPLA.

2.3. Location

(1) Department of Thoracic Surgery, Sokolowski Pulmonary Hospital, Zakopane, Poland.

2.4. Patients

2.4.1. Inclusion criteria

A group of consecutive patients with cytological or histological diagnosis of NSCLC, clinical stage I—III based on medical history, physical examination, chest X-ray, CT of the chest and upper abdomen, abdominal ultrasound and bronchoscopy. Patient’s general condition must enable appropriate pulmonary resection, based on the following criteria: general performance status 0 or 1 according to WHO (Zubrod) scale, forced expiratory volume (FEV1) ≥ 1.3 l (lobectomy) or ≥ 1.8 l (pneumonectomy), stair climbing test ≥2 floors (lobectomy) or ≥3 floors (pneumonectomy).

2.4.2. Exclusion criteria

History of other malignancy, histological confirmation of small-cell lung cancer, confirmation of metastatic mediastinal lymph nodes using the transbronchial needle aspiration biopsy, history of thoracotomy or sternotomy or lack of informed consent.

2.5. Intervention

Randomization was performed on phone request, out of our institution, using computer-generated random numbers. Patients were allocated to the TEMPLA group or to the CM group. The technique of the TEMPLA was described in detail elsewhere [1]. In brief: using a 6 cm collar incision in the lower neck both common carotid arteries are dissected free and the recurrent nerves are identified using a previously described method [2]. The station 1 nodes, lying above the left innominate vein are removed. retracting the innominate artery to the left side, the right paratracheal space is opened and its content (stations 2R and 4R) is dissected using a peanut-sponge to the level below the azygos vein. Next, the trachea is retracted to the right side and the left paratracheal nodes (stations 2L and 4L) are dissected to the level of 1/3 of the left main bronchus, carefully preserving the left laryngeal recurrent nerve. Using the Wolf mediastinoscope to retract the pulmonary artery upwards, subcarinal and paraesophageal nodes (stations 7 and 8) are dissected. Next, the plane between the left common carotid artery and the left internal jugular vein is developed, the artery and the aortic arch is retracted downwards and the paraaortic and aorto-pulmonary window (stations 6 and 5) nodes are removed. The last step is dissecting the anterior surface of the confluence of innominate veins and the superior vena cava and removal of the prevascular (station 3A) nodes. The whole dissection is performed in the open fashion, using standard instruments. The wound is closed without leaving any drain.

The mediastinoscopy was performed in the standard manner, except for a longer incision. We used the Wolf operating videodendroscopy (Richard Wolf GmbH, Germany).

The patients without metastases in mediastinal nodes were re-assessed for their general fitness using the same criteria as previously, and scheduled for the definite surgery.

2.6. Variables measured

The variables recorded were: (1) the arterial blood gas analysis (pH, pO2, pCO2, standard bicarbonate (SB) and base excess (BE)) and (2) the spirometric parameters (vital capacity (VC), first-second forced expiratory volume (FEV), FEV1/VC), measured preoperatively and on postoperative day 1, 3, and 5, (3) the diffusing capacity of lung for carbon monoxide (DLCO) and lung compliance measured preoperatively and on the postoperative day 3—5 and (4) respiratory complications. For blood gas analysis we used the Ciba-Corning 248 analyzer (Ciba Corning Diagnostics Ltd., UK), for spirometric parameters we used the Pneumo RS spirometer (Artmed, Poland), for compliance measurements—the Jaeger MesterLab (Jaeger-Toennies GmbH, Germany) and for DLCO—Jaeger MasterScereen PFT apparatus (Jaeger-Toennies GmbH, Germany).

All complications related to the respiratory system were recorded.

2.7. Statistical analysis

Endpoints and clinical variables were recorded using a chart designed especially for the study. The statistical analysis was performed using the STATISTICA 6.1 PL software package.

The univariate analysis (ANOVA) was used to assess changes in time, and if the effect was significant the post hoc Tukey test was used to compare the mean values. Comparisons between two groups was performed using the Student’s t-test. The 95% confidence interval (CI) was calculated for all variables. For analysis of the qualitative variables the \( \chi^2 \) Pearson test was used (if the groups were small, the exact Fisher test was used).

The level of significance was set at 0.05.

3. Results

Initially, the number of 100 patients was planned to be enrolled in the study. However, the interim analysis has shown a significantly greater number of false-negative results of standard mediastinoscopy comparing with the TEMPLA, leading to the primary pulmonary resections in patients with N2 disease. Due to these results (being a subject of a separate publication), we decided to terminate the enrollment for
ethical reasons. So, data of 41 patients was available for analysis.

3.1. Patients characteristics in the TEMLA group and the CM group

There were 21 (19 men) patients randomized to the TEMLA group and 20 (all men) to the mediastinoscopy group. Mean age in the TEMLA group was 62 (range: 47—76) and in the CM group 59 (range: 46—73). Groups were comparable regarding patients age ($p = 0.264$; Student’s $t$-test), gender ($p = 0.256$; Student’s $t$-test), general performance status according to the WHO scale ($p = 0.355$; exact Fisher test), the baseline FEV1 ($p = 0.826$; Student’s $t$-test), stair climbing test ($p = 0.368$; $\chi^2$ Pearson test), and co-morbidity, including hypertension, coronary artery disease, history of myocardial infarction, circulatory insufficiency, peripheral artery disease, chronic pulmonary obstructive disease, diabetes and renal insufficiency ($p = 0.319—0.743$; exact Fisher test).

3.2. Comparison of pulmonary ventilation

On the 1st postoperative day there was a significant decrease in VC and FEV1 observed, with a subsequent increase in the next days; such effect was not observed for FEV1/VC and lung compliance (Fig. 1). The aforementioned changes of all the analyzed parameters were similar in the TEMLA group and the mediastinoscopy group: the differences in the postoperative days 1, 3, and 5 were not significant (Table 1).

![Spirometric values preoperatively and in the postoperative days 1, 3, and 5, and lung compliance preoperatively and in the postoperative days 3–5 in the TEMLA group (dotted line) and mediastinoscopy group (continuous line).](https://academic.oup.com/ejcts/article-abstract/31/2/161/451770)

**Fig. 1.**

**Table 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TEMLA group mean value (95% CI)</th>
<th>Mediastinoscopy group mean value (95% CI)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC preoperative</td>
<td>3.31 (3.00—3.61)</td>
<td>3.33 (2.99—3.67)</td>
<td>1.00a</td>
</tr>
<tr>
<td>VC 1st day</td>
<td>2.38 (2.08—2.69)</td>
<td>2.53 (2.16—2.89)</td>
<td>0.99a</td>
</tr>
<tr>
<td>VC 3rd day</td>
<td>2.46 (2.19—2.74)</td>
<td>2.84 (2.51—3.17)</td>
<td>0.98a</td>
</tr>
<tr>
<td>VC 5th day</td>
<td>2.70 (2.42—2.98)</td>
<td>3.02 (2.61—3.44)</td>
<td>0.99a</td>
</tr>
<tr>
<td>FEV1 preop</td>
<td>2.29 (2.03—2.56)</td>
<td>2.37 (2.10—2.64)</td>
<td>0.99a</td>
</tr>
<tr>
<td>FEV1 1st day</td>
<td>1.69 (95% CI: 1.49—1.88)</td>
<td>1.73 (95% CI: 1.44—2.02)</td>
<td>0.99a</td>
</tr>
<tr>
<td>FEV1 3rd day</td>
<td>1.75 (95% CI: 1.51—1.96)</td>
<td>2.05 (95% CI: 1.76—2.33)</td>
<td>0.98a</td>
</tr>
<tr>
<td>FEV1 5th day</td>
<td>1.96 (95% CI: 1.77—2.14)</td>
<td>2.20 (95% CI: 1.92—2.49)</td>
<td>0.98a</td>
</tr>
<tr>
<td>FEV1/VC preop</td>
<td>70.1% (63.4—76.8)</td>
<td>73.0 (95% CI: 66.8—79.1)</td>
<td>0.89 b</td>
</tr>
<tr>
<td>FEV1/VC 1st day</td>
<td>72.3 (95% CI: 66.0—78.5)</td>
<td>70.7 (95% CI: 63.0—78.4)</td>
<td></td>
</tr>
<tr>
<td>FEV1/VC 3rd day</td>
<td>70.9 (95% CI: 63.2—78.6)</td>
<td>69.5 (95% CI: 63.4—75.8)</td>
<td></td>
</tr>
<tr>
<td>FEV1/VC 5th day</td>
<td>73.7 (95% CI: 67.7—79.6)</td>
<td>73.8 (95% CI: 68.2—79.4)</td>
<td></td>
</tr>
<tr>
<td>Compliance preop</td>
<td>3.73 (95% CI: 2.15—5.32)</td>
<td>2.73 (95% CI: 1.5—3.96)</td>
<td>0.38 b</td>
</tr>
<tr>
<td>Compliance 3–5 day</td>
<td>4.19 (95% CI: 1.73—6.65)</td>
<td>3.04 (1.14—4.95)</td>
<td></td>
</tr>
</tbody>
</table>

The VC and FEV1 values are expressed in liters (l), and compliance in liters per kilopascal (l/kPa).

* HSD Tukey test.

b Analysis of variance.
3.3. Comparison of arterial blood gas pressures

There was a slight decrease observed in pH, SB, and BE on the 1st postoperative day, followed by an increase on the 3rd day and normalization thereafter. The pO2 dropped on the 1st day and subsequently returned to the normal values, whereas with pCO2 no characteristic pattern of changes was noted (Fig. 2A–E). The aforementioned changes of all the analyzed parameters were similar in the TEMLA group and the mediastinoscopy group: the differences of blood gas values on postoperative days 1, 3, and 5 were not significant (Table 2).

3.4. Comparison of pulmonary diffusion

There was no characteristic pattern of DLCO changes (Fig. 2F); the differences of DLCO values on postoperative day 3–5 in both groups were not significant (Table 3).

3.5. Comparison of respiratory complications

There were no postoperative deaths and only one respiratory insufficiency, requiring ventilatory support for 2 days, occurring in a patient from the TEMLA group. Using the exact Fisher test we did not find a significant difference between groups regarding this complication ($p = 0.512$). Among the 14 patients with negative result of the TEMLA only one was found unfit for the definite surgery, the same for one patient out of 17 in the CM group.

4. Discussion

The cervical mediastinoscopy has been the gold standard technique of surgical mediastinal staging in NSCLC patients and there is a large body of evidence showing its safety [3–6]. However, the sensitivity and the negative predictive value of this technique are not optimal, mainly due to numerous stations of mediastinal nodes (1, 3A, 3P, 5, 6, 8, 9) being out of the reach of the mediastinoscopy. Several techniques were proposed to enable access to these nodes, including extended cervical mediastinoscopy, anterior mediastinotomy, VATS biopsy and transesophageal or transbronchial needle aspiration biopsy—none of them fulfilling the criteria of the ideal model of staging procedure, characterized in the Introduction section. The TEMLA technique is closer to this model than any other staging modality, and data confirming its significant superiority over the mediastinoscopy in NSCLC.
staging has been presented by us at the 5th EASTS/ESTS Joint Meeting, Stockholm, 2006. Assessment of both, ventilation and diffusion capacity alterations, combined with comparison of related complications, enables a comprehensive analysis of the respiratory side-effects of TEMLA compared to mediastinoscopy, being the ‘gold standard’ technique of proven safety.

The way, in which bilateral mediastinal lymphadenectomy could theoretically cause impairment of ventilation, is decreased lung compliance due to the lymphatic congestion in the interstitial space of the lung. We decided to measure directly this parameter, besides the standard spirometric values, which may be biased by the effect of increased respiratory work, compensating the loss of lung compliance. As we have not found any significant difference between both groups in the direct measurements of lung compliance, nor in the standard spirometric parameters, the conclusion that TEMLA does not produce any clinically important changes in the ventilation of the lungs, seems justified.

The theoretical congestion of lymph in the interstitial space of the lung might also decrease gas exchange as a result of impairment of diffusion across the alveolar-capillary membrane. The blood gas analysis is one of the most useful clinical methods for assessment of function of the respiratory system, but it is not a specific parameter for ventilation nor for diffusion capacity. Besides the diffusion and ventilation, blood gas analysis reflects other factors influencing the $O_2$ and $CO_2$ partial pressures in the arterial blood. For this reason, to assess diffusion capacity we used the DLCO measurements, being more specific and very sensitive modality, enabling detection even of subclinical alterations in gas diffusion across the alveolar-capillary membrane [7]. Although data regarding relation between pulmonary lymphatic edema and lung diffusion capacity are lacking, the effect of thickening of the alveolar membrane on diffusing capacity in patients with congestive heart disease has been described [8–10]. As there is a relationship between resting DLCO and hemoglobin concentration [11], we used the standardized values according to the actual hemoglobin. The measurements were performed on the rest to avoid a bias that might be caused by the cardiac output changes [12,13]. As our results failed to show any significant difference in both, DLCO and the standard blood gas indices, we drew the conclusion that the TEMLA does not cause any clinically important impairment of gas exchange in the lungs.

The third part of our analysis was comparison of respiratory complications associated with the TEMLA. As the respiratory insufficiency developed only in one patient, any reasonable comparison is not possible. This is due to the low complication rate associated with mediastinoscopy [3–6], as well with the TEMLA [1]. In our initial series of 83 patients there were only one respiratory insufficiency, requiring use of a ventilator [1]. The unplanned termination of enrollment to the study, explained in Section 3, was the

![Table 3](https://academic.oup.com/ejcts/article-abstract/31/2/161/451770)

**Table 3**
<table>
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<th>Mediastinoscopy group mean value (95% CI)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLCO preoperative</td>
<td>1.26 (1.15–1.36)</td>
<td>1.23 (1.09–1.36)</td>
<td>0.91*</td>
</tr>
</tbody>
</table>
reason for the limited number of patients available for analysis. Nevertheless, the difference between the groups regarding respiratory complications, as assessed using the exact Fisher test, was not significant.

The relatively small number of patients is undoubtedly the drawback of our study. Unfortunately, due to the ethical reasons explained in Section 3, it could not be greater.

Although the follow-up was only 5 days, we have shown, that after some decrease on the 1st postoperative day, the VC, FEV₁, pH, pO₂, SB and BE values returned to the preoperative level before the 5th day after the procedure, and for pCO₂, DLCO and compliance no noticeable decrease was observed. It is unlikely that — after normalization of the respiratory parameters — they could deteriorate again in a more distant future. The long-term follow-up does not therefore seem to be necessary. Moreover, form the practical point of view, the most important is restoration of the patient’s fitness about one week after the TEMLA, when the definite pulmonary resection is to be performed.

The study elucidated one of our main concerns regarding TEMLA, namely the risk of deterioration of pulmonary function that might prevent the curative pulmonary resection. Our present results (1/21 patients who underwent TEMLA was unfit for thoracotomy) show that the risk is not greater than after standard CM (1/20 unfit for thoracotomy). So, the relatively large proportion of patients unfit for pulmonary resection after the TEMLA (12/83) found in our initial series is attributable to the excessively liberal inclusion criteria for TEMLA we have been using previously.

5. Conclusions

We conclude, that complete excision of mediastinal lymph nodes stations 1, 2R, 2L, 3A, 4R, 4L, 5, 6, 7, and 8 (TEMLA) is not associated with greater incidence of respiratory insufficiency and does not increase the number of patients unfit for subsequent pulmonary resection, compared to standard mediastinoscopy. Moreover, the TEMLA procedure does not produce greater alterations in lung ventilation nor gas diffusion across the alveolar-capillary membrane, compared to standard mediastinoscopy.

References


Appendix A. Conference discussion

Dr M. Beshay (Bielefeld, Germany): Could you please tell us how you reach the 5th and the 6th lymph node stations from the transcervical approach?

Dr Kuzdzal: Yes. We perform a nodal dissection, including on the right side stations 3A, 2R, 4L, 7, and 9, and on the left side, 5, 6, 7, and 8.

Dr M. Beshay (Bielefeld, Germany): If I remember correctly from what you’ve said in previous talks, at the time of thoracotomy you perform systematic nodal dissection, don’t you?

Dr Kuzdzal: Yes. We perform a nodal dissection, including on the right side stations 3A, 2R, 4L, 7, 8, and 9, and on the left side, 5, 6, 7, and 8.

Dr M. Beshay (Bielefeld, Germany): The technique of exploring the aorto-pulmonary window and preaortic nodes is so that we develop a plane between the left common carotid artery and the left common jugular vein, and dissecting along this plane, we reach the anterior surface of the aortic arch. Then, retracting the vein upwards and the aortic arch and common carotid artery downwards, we have a good enough approach to the nodes station 6 and aorto-pulmonary window, and even deeper into the mediastinum: we are able to reach the level of the superior pulmonary vein and clear this space from all the nodes. This presentation was not aimed at presenting the technique, so this is only an outline of it.