Non-small-cell lung cancer restaging with transcervical extended mediastinal lymphadenectomy

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Abstract

Background: To analyse a diagnostic yield of the transcervical extended mediastinal lymphadenectomy (TEMLA) in restaging of the mediastinal nodes after neoadjuvant chemo- or chemo-radiotherapy for non-small-cell lung cancer (NSCLC).

Methods: From 1 January 2004 to 30 April 2009, 63 patients who underwent induction chemotherapy or chemo-radiotherapy for N2 and N2/3 metastatic nodes discovered preoperatively were restaged. There were 12 women and 51 men in the age group of 43–71 (mean 57.8) years. There were 45 squamous cell carcinomas, 13 adenocarcinomas, one pleomorphic carcinoma and four NSCLCs. A total of 54 patients underwent neoadjuvant chemotherapy and nine chemo-radiotherapy. Seven patients had mediastinoscopy before neoadjuvant therapy. As many as 34 patients underwent endobronchial ultrasound (EBUS), one patient underwent endo-oesophageal ultrasound (EUS) and 10 patients underwent combined EBUS/EUS. The diagnostic results of TEMLA were compared with the results of the largest published series of restaging patients. The results of subsequent thoracotomies after negative TEMLA were presented.

Results: There were no serious complications or mortality after TEMLA. Metastatic nodes were discovered in 22 patients including three patients with N3 nodes and 19 patients with N2 nodes. Stations 7, 4R, 2R and 4L were the most prevalent. Of the 63 patients, 42 underwent subsequently thoracotomy. Resectability for negative TEMLA was 92.7%. There were 37 R0 resections and four R1 resections. There was no postoperative mortality, two bronchial fistulas were developed (after inferior bilobectomy and right pneumonectomy; the second one healed spontaneously) and there were no other serious complications. During thoracotomy with completion lymphadenectomy one false-negative result was found (single node in station 8). Sensitivity of TEMLA in the discovery of N2/3 nodes during restaging was 95.5%, specificity 100%, accuracy 98.3%, negative predictive value (NPV) 97.4% and positive predictive value (PPV) 100%. TEMLA was found to have significantly better sensitivity and NPV ($p < 0.05$) than other series of restaging. During follow-up a local recurrence was noted in six of 37 (15.7%) patients after pulmonary resection.

Conclusions: (1) The results of TEMLA in restaging of NSCLC (N2/3) patients after induction chemotherapy or chemo-radiotherapy were significantly better than those achieved with remediastinoscopy, EBUS and positron emission tomography/computed tomography (PET/CT). (2) The results of future studies will show if TEMLA should be considered the gold standard of mediastinal nodal restaging after neoadjuvant therapy in patients with NSCLC.

Guidelines of American College of Chest Physicians (ACCP 2007), concurrent chemo-radiation is the recommended treatment in stage IIIA NSCLC. In NSCLC patients with N2 disease identified preoperatively, induction therapy followed by surgery is not recommended except as part of a clinical trial [4]. This statement was based on the results of two big multi-institutional trials presented recently (EORTC and North American Intergroup 0139 (RTOG 9309)), reporting no statistically significant difference of survival in patients randomised to the chemo-radiotherapy and induction chemo- or chemo-radiotherapy followed by surgery [5–7]. However, in these reports a substantial number of patients were found not to have a downstaging to NO–1 after induction therapy. The results of survival in patients

Keywords: Lung cancer; Mediastinal lymph nodes

1. Introduction

The role of surgery in the multimodality treatment is still a matter of discussion. Until recently, neoadjuvant chemotherapy with subsequent pulmonary resection was regarded the standard of treatment for patients with N2 metastatic nodes discovered preoperatively [1–3]. However, this view has been changed currently and, according to the current

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downstaged to N0–1 were significantly better than those in whom residual N2 metastatic nodes were found and in patients treated with radical chemo-radiotherapy without operation.

In addition, recent systematic review and meta-analysis of the literature showed that the results of treatment of patients with NSCLC in stage IIIA were significantly better than those treated with surgery alone [8]. These controversies underline the critical role of proper restaging of the mediastinal nodes after neoadjuvant therapy and indicate that inclusion of surgery in the treatment protocol might be probably beneficial for the properly selected patients. The choice of the optimal methods used for restaging remains the problem for discussion. In this retrospective study, we report our results of restaging of the mediastinal nodes with the transcervical extended mediastinal lymphadenectomy (TEMLA), the new surgical technique introduced by our team in 2004 [9,10].

2. Material and methods

A total of 63 patients who underwent induction chemotherapy or chemo-radiotherapy for N2 and N2/3 metastatic nodes discovered preoperatively were restaged from 1 January 2004 to 30 April 2009.

There were 12 women and 51 men in the age group 43–71 (mean 57.8) years. There were 45 squamous cell carcinomas, 13 adenocarcinomas, one pleomorphic carcinoma and four NSCLCs. Among these patients: 54 patients underwent neoadjuvant chemotherapy and nine chemo-radiotherapy. Seven patients had mediastinoscopy before neoadjuvant therapy. The diagnosis of N2/3 metastatic involvement before neoadjuvant chemotherapy was confirmed with the positive results of invasive staging in 27 patients including seven patients who underwent mediastinoscopy, 16 patients who underwent EBUS and four patients who underwent EUS. In the other 36 patients the diagnosis of N2/3 was based on the results of chest CT. Of these 36 patients, four were initially staged in our hospital before EBUS and EUS became available and 30 patients were initially staged elsewhere.

PET/CT was not performed in this group of patients. After completion of neoadjuvant therapy all patients were restaged with chest CT. In all patients from the study group there was a partial or complete response estimated by chest CT. Patients with bulky mediastinal nodes on restaging CT were included only if restaging with EBUS/EUS was negative. EBUS was performed in 34 patients, EUS in one patient and combined EBUS/EUS in 10 patients. All patients underwent TEMLA.

The technique of TEMLA has been described in detail elsewhere and was used for restaging in a similar manner to the one used for primary staging [9,10]. In brief, it included a 5- to 8-cm collar incision in the neck, elevation of the sternal manubrium with a special retractor, bilateral visualisation of the laryngeal recurrent and vagus nerves and dissection of all mediastinal nodal stations except for the pulmonary ligaments nodes (station 9). Most of the procedure was performed in the open fashion, with the subcarinal and the peri-oesophageal nodes (stations 7 and 8) removed in the mediastinoscopy-assisted technique and the para-aortic and the pulmonary-window nodes (stations 6 and 5) removed in the video-assisted thoracic surgery (VATS), with the videothoracoscope inserted through the transcervical incision. In general, the mediastinal pleura was not violated and no drain was left in the mediastinum. All patients with negative results of TEMLA, who were fit enough, were referred to thoracotomy and radical pulmonary resection with completion systematic nodal dissection. Pathological examinations were performed in a standard haematoxilin/eosin (HE) staining technique. The diagnostic yield of TEMLA was calculated in the standard manner. The results of restaging with TEMLA were compared with the results of the other biggest reported series of patients restaged with the other techniques.

Statistical analysis was performed with the STATISTICA software package. Probability values were generated with the chi-square test and the Student’s t-test or the Mann–Whitney test. Probability values $p < 0.05$ were considered to be statistically significant. The study was approved by the Scientific Committee of our institution.

3. Results

On restaging after neoadjuvant therapy performed in our hospital, metastatic nodes were found with EBUS in three patients, with EUS in one patient and in combined EBUS/EUS in two patients (overall six patients). These patients were not excluded from TEMLA because they were suspected to have very limited extent of the mediastinal nodal involvement without any other signs of metastatic spread. There were no serious complications or mortality after TEMLA. Metastatic nodes were discovered in 22 patients including three patients with N3 nodes and 19 patients with N2 nodes.

Stations 7, 4R, 2R and 4L were most prevalent. In two out of six patients, who had positive results of restaging with EBUS or/and EUS, single metastatic encapsulated nodes were found on TEMLA, which were removed without laceration of the nodal capsule. These patients underwent subsequent pulmonary resection. In the other four patients, the multi-level metastatic nodal involvement was found. These patients were excluded from further thoracotomy.

In two patients N3 supraclavicular nodes were found before neoadjuvant therapy. These nodes disappeared after neoadjuvant therapy, which was confirmed with TEMLA with simultaneous bilateral supraclavicular nodal dissection (there were no metastatic nodes found). These two patients underwent subsequently pulmonary resection. The other five patients in whom N3 nodes were discovered on TEMLA did not undergo pulmonary resection.

The downstaging rate to N0/1 achieved in 27 patients in whom metastatic N2/3 nodes were confirmed with pretreatment EBUS, EUS or mediastinoscopy was 59.3% (16/27 patients).

Of the 41 patients, 38 had negative result of TEMLA and four patients with positive single station, encapsulated, completely removed N2 nodes, who underwent subsequent-thoracotomy. Two of four of these patients were positive on EBUS/EUS, as described earlier; two others were negative on EBUS/EUS but positive on TEMLA. There were 41 pulmonary resections (and one exploratory thoracotomy) including: 20
Table 1
Types of pulmonary resections in 42 patients operated on after negative result of TEMLA.

<table>
<thead>
<tr>
<th>Type of pulmonary resection</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonectomy</td>
<td>20 (10 right, 10 left)</td>
</tr>
<tr>
<td>Sleeve-lobectomy</td>
<td>2</td>
</tr>
<tr>
<td>Bilobectomy</td>
<td>6</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>13</td>
</tr>
<tr>
<td>Exploratory thoracotomy</td>
<td>1</td>
</tr>
<tr>
<td>Overall</td>
<td>42</td>
</tr>
</tbody>
</table>

The unsatisfactory methods of restaging most probably affected the survival rates in this group of patients ranging from 0% to 24% [17,18]. Therefore, the results and conclusions of both studies must be treated with caution.

During thoracotomy with completion lymphadenectomy, one false-negative result was found (single node of the station 8). Sensitivity of TEMLA in discovery of N2/3 nodes during restaging was 95.7%, specificity was 100%, accuracy was 98.4%, NPV was 97.6% and PPV was 100% (Table 2). Three

Table 2
Diagnostic yield of TEMLA in restaging of NSCLC.

<table>
<thead>
<tr>
<th>Diagnostic parameter</th>
<th>Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>95.7</td>
</tr>
<tr>
<td>Specificity</td>
<td>100</td>
</tr>
<tr>
<td>Negative predictive value (NPV)</td>
<td>97.6</td>
</tr>
<tr>
<td>Positive predictive value (PPV)</td>
<td>100</td>
</tr>
<tr>
<td>Accuracy</td>
<td>98.4</td>
</tr>
</tbody>
</table>

The results of recently published randomised controlled trials of resection versus radiotherapy after induction chemotherapy or chemotherapy and radiotherapy showed no statistically significant difference of overall survival between surgery and radiotherapy [5,6]. The problems with results of both studies were that the results of patients with and without metastatic nodal downstaging after neoadjuvant therapy were reported together.

In both studies the survival rates were significantly better in patients in whom downstaging to N0/1 was achieved than in patients with persistent N2 disease. In this selected group of patients with yN0/1 disease, there was a significant benefit of surgical treatment combined with induction chemotherapy or chemo-radiotherapy in comparison to the group of patients treated with chemo-radiotherapy without surgery. Similar conclusions were made by the authors of the other studies [15,16].

Unfortunately, the number of patients with persistent N2 nodes after induction treatment was exceedingly high in RTOG 9309 Study (36%) and in the EORTC 08941 study (58%), which most probably has affected the survival rates of the entire groups.

The results of other studies showed that the results of treatment of patients with residual N2 nodes after neoadjuvant therapy were controversial, with reported 5-year survival rates in this group of patients ranging from 0% to 24% [17,18]. Therefore, the results and conclusions of both studies must be treated with caution.

The unsatisfactory methods of restaging most probably negatively affected the results with final conclusion of RTOG 9309 Study group and EORTC group that chemo-radiotherapy was the standard treatment for future EORTC trials in stage IIIA NSCLC, which was repeated in the recent ACCP guidelines. Selection of the subgroup of patients with N2 nodes

4. Comment

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Table 3
Results of remediastinoscopy.

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>% Sensitivity</th>
<th>% Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rami-Porta et al. [18]</td>
<td>48</td>
<td>83</td>
<td>91</td>
</tr>
<tr>
<td>De Waele et al. [24]</td>
<td>32</td>
<td>71</td>
<td>84</td>
</tr>
<tr>
<td>De Leyn et al. [22]</td>
<td>30</td>
<td>29</td>
<td>60</td>
</tr>
<tr>
<td>De Waele et al. [11]</td>
<td>104</td>
<td>71</td>
<td>84</td>
</tr>
<tr>
<td>Marra et al. [12]</td>
<td>104</td>
<td>61</td>
<td>88</td>
</tr>
</tbody>
</table>

Table 4
Diagnostic yield of the largest reported series of restaging of NSCLC.

<table>
<thead>
<tr>
<th>De Waele et al. (group 1)</th>
<th>Marra et al. (group 2)</th>
<th>Herth et al. (group 3)</th>
<th>Cerfolio et al. (group 4)</th>
<th>Zielinski et al. (group 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive (TP)</td>
<td>40</td>
<td>20</td>
<td>89</td>
<td>21</td>
</tr>
<tr>
<td>True negative (TN)</td>
<td>47</td>
<td>71</td>
<td>7</td>
<td>52</td>
</tr>
<tr>
<td>False positive (FP)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>False negative (FN)</td>
<td>17</td>
<td>13</td>
<td>28</td>
<td>13</td>
</tr>
<tr>
<td>Overall</td>
<td>104</td>
<td>104</td>
<td>124</td>
<td>93</td>
</tr>
</tbody>
</table>

Comparison of sensitivity: Groups 1–5, p = 0.0156; Groups 2–5, p = 0.0043; Groups 3–5, p = 0.0357; Groups 4–5, p = 0.0051. Comparison of NPV: Groups 1–5, p = 0.0018; Groups 2–5, p = 0.0332; Groups 3–5, p = 0.0000; Groups 4–5, p = 0.0105.
downstaged to yN0/1 nodes by means of reliable restaging method is therefore the most important issue.

Currently available methods of restaging of the mediastinum include imaging studies, endoscopic studies and surgical techniques. Imaging studies include CT, which has relatively low diagnostic yield (sensitivity 41—59%, specificity 62—75% and accuracy 58—60%) and PET/CT with sensitivity 61—77%, specificity 85—90% and accuracy 78—83% [14,19]. PET/CT was found to be superior to CT (accuracy 89% vs 36% for stage I) [14].

Restaging with endoscopic techniques include EBUS, EUS and combined EBUS/EUS. EBUS was used in the multi-institutional report (Copenhagen, Boston, Heidelberg, Chiba) on 124 patients restaged after induction therapy with sensitivity 76%, specificity 100% and accuracy 83% [21]. Surgical techniques of restaging include repeated mediastinoscopy (remediastinoscopy), VATS and TEMLA. Several series of remediastinoscopy are shown in Table 3. In general, remediastinoscopy seems to be a technique of moderate diagnostic yield with sensitivity of 61—83% (with the exception of sensitivity 29% in the study published by De Leyn et al. [22]). There was only one study on restaging with VATS. The study group included 70 patients but in 17 of them, procedures could not be completed due to adhesions. The authors reported sensitivity 75% and specificity 100% [23].

The current study is the first one presenting the use of TEMLA for the restaging of the mediastinal nodal nodes. We did not rely on the restaging chest CT because of its low diagnostic yield. Our results of restaging with EBUS—transbronchial needle aspiration (TBNA) published elsewhere showed sensitivity 66.7% and NPV 77.5% [20]. The results of our study show very high diagnostic yield of TEMLA in the restaging of the mediastinal nodes, with sensitivity of 95.7% and NPV of 97.6%. Despite some fibrosis of the mediastinum after induction therapy, especially in patients who underwent chemo-radiotherapy, the technical difficulties of an operation could be managed without any special problems. The full range of nodal dissection was performed in all patients and there were no intra-operative or postoperative complications. A false-negative result was found in only one patient with the omission of a single metastatic node from station 8. In the rest of the 62 of 63 patients the results of TEMLA were correct, which was proven by subsequent thoracotomy with completion lymphadenectomy. The use of TEMLA enabled proper selection of patients for thoracotomy with high resectability rate of 92.7%, no mortality and relatively low morbidity. The occurrence of two post-operative bronchial fistulas indicated a higher operative risk in patients undergoing pulmonary resection after neoadjuvant therapy. Our indications for TEMLA were very liberal, including two patients with proven N3 supraclavicular nodes discovered before neoadjuvant treatment. In our opinion there were no absolute contraindications to carry out TEMLA with bilateral supraclavicular nodal dissection performed with transcervical incision used for TEMLA. After obtaining negative results of TEMLA and supraclavicular nodal dissection, we decided that subsequent thoracotomy was justified. We are aware that this was not a standard way to treat patients at stage IIIB NSCLC. The downstaging rate to N0/1 in our study was 65.1%, very similar to the RTOG 9309 Study (64%). We must stress, however, that in 36 of 63 patients, the diagnosis of N2/3 nodal metastasis was based only on chest CT, without confirmation by invasive staging. Most of these patients were initially diagnosed in other institutions. At least in some of these patients, the pretreatment diagnosis of N2/3 might have been false positive. The downstaging rate to N0/1 achieved in patients in whom metastatic N2/3 nodes were confirmed with pretreatment EBUS, EUS or mediastinoscopy was 59.3%. The presented results of restaging with TEMLA are significantly better than those of any other diagnostic technique used for restaging, including such promising modalities as PET/CT and endoscopic ultrasonography (EBUS and EUS). However, our series of patients, including only seven of 63 patients who underwent mediastinoscopy before starting neoadjuvant treatment, was different from the series of de Waele et al. and Marra et al., including patients all of whom underwent previous mediastinoscopy. It must be stressed that in our experience the technical difficulty of restaging with TEMLA in patients with or without previous mediastinoscopy was quite similar. In none of the patients in our series who underwent previous mediastinoscopy was there any false-negative result during restaging. A prospective study comparing the results of restaging with CT, PET/CT, combined EBUS/EUS and TEMLA will soon be underway. The results of such a trial will provide the final answer as to whether TEMLA should be regarded the gold standard for restaging of the mediastinum after neoadjuvant therapy in patients with NSCLC instead of mediastinoscopy, which has been considered the current standard by the recent ESTS guidelines [25].

5. Conclusions

1. The results of our study showed very high diagnostic value of TEMLA in the restaging of NSCLC (N2) patients after induction chemotherapy or chemo-radiotherapy, significantly better than those achieved with mediastinoscopy, EBUS and PET/CT.

2. The results of future studies will show if TEMLA should be considered the gold standard of mediastinal nodal restaging after neoadjuvant therapy in patients with NSCLC.

References


Different methods exist for mediastinal restaging after induction therapy. These include non-invasive techniques such as computed tomography (CT), magnetic resonance imaging and positron emission tomography; minimally invasive techniques comprising transbronchial needle aspiration (TBNA), endobronchial ultrasound (EBUS) and endoscopic oesophageal ultrasound (EUS); and invasive techniques as mediastinoscopy and video-assisted thoracic surgery (VATS) [1]. For restaging, non-invasive techniques have a rather low sensitivity and specificity and the false-negative rate of minimally invasive techniques remains high.

Repeat mediastinoscopy provides larger tissue biopsies but is technically more difficult and has a lower accuracy than a first mediastinoscopy. Experience with VATS for restaging is limited at the present time. Therefore, the best available method for restaging after induction therapy remains a highly debated issue as no currently available technique can be considered to be the gold standard. Nevertheless, down-staging is a major prognostic factor in patients with locally advanced non-small cell lung cancer and patients with persisting mediastinal involvement after induction therapy have a poor prognosis [2–4].

Editorial comment

Mediastinal restaging: has the Holy Grail been found?

Keywords: Lung cancer; Restaging; Induction therapy; TNM classification