Accuracy and survival of repeat mediastinoscopy after induction therapy for non-small cell lung cancer in a combined series of 104 patients

Michèle De Waele a,*, Mireia Serra-Mitjans b, Jeroen Hendriks a, Patrick Lauwers a, José Belda-Sanchis b, Paul Van Schil a, Ramon Rami-Porta b

a Department of Thoracic and Vascular Surgery, University Hospital of Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium
b Department of Thoracic Surgery, Hospital Mutua de Terrassa, Plaza Dr. Robert 5, 08221 Terrassa, Spain

Received 13 September 2007; received in revised form 5 February 2008; accepted 6 February 2008; Available online 14 March 2008

Abstract

Objective: Precise restaging of non-small cell lung cancer after induction therapy is of utmost importance. Remediastinoscopy remains a controversial procedure. In a combined, updated series of two thoracic centres, accuracy and survival of remediastinoscopy were determined.

Methods: From November 1994 to August 2005, remediastinoscopy was performed in 104 patients (98 men, 6 women) after induction therapy for locally advanced non-small cell lung cancer. Mean age was 64.3 years (range 38—85). Neoadjuvant chemotherapy was given in 79 patients and chemoradiotherapy in 25. Follow-up data were completed in January 2007.

Results: Remediastinoscopy was technically feasible in all patients except for one who died due to perioperative haemorrhage. Remediastinoscopy was positive in 40 patients and negative in 64; the latter group underwent thoracotomy. There were 17 false-negative remediastinoscopies. Sensitivity of remediastinoscopy was 71%, specificity 100% and accuracy 84%. Follow-up was complete for all patients. Sixty-nine died, mostly of distant metastases. Median survival time for the whole group was 18 months (95% confidence interval 11—25). Median survival time in patients with a positive remediastinoscopy was 14 months (95% confidence interval 8—20), with a negative remediastinoscopy 28 months (95% confidence interval 15—41) and with a false-negative remediastinoscopy 24 months (95% confidence interval 3—45). In univariate analysis the difference between positive and negative remediastinoscopies was highly significant (p = 0.001). In a multivariate analysis including sex, age, histology, centre, and nodal status at remediastinoscopy, only nodal status was a significant independent prognostic factor (p = 0.008).

Conclusions: Remediastinoscopy is a valuable restaging procedure after induction therapy. Persisting mediastinal nodal involvement proven at remediastinoscopy heralds a poor prognosis.

© 2008 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.

Keywords: Remediastinoscopy; Lung cancer; Staging; Induction therapy

1. Introduction

Restaging procedures for non-small cell lung cancer (NSCLC) after induction chemotherapeutic or chemoradiotherapy remain controversial as minimally invasive procedures become available. Although mediastinal fibrosis renders a mediastinoscopy technically more difficult than the initial one, this invasive procedure has shown to be feasible for a variety of indications [1—4]. After neoadjuvant therapy, mediastinoscopy remains a valuable tool in restaging locally advanced NSCLC [5,6]. It provides histological evidence of response after induction therapy and selects those patients who will most likely benefit from a subsequent thoracotomy. Up to now mainly smaller series on mediastinoscopies after induction therapy, including three with survival analysis, have been reported in literature [1,7,24].

We updated our results and combined them with another dedicated thoracic centre to study whether results were consistent in a larger series. In this way, a more meaningful survival analysis is obtained together with independent prognostic factors for survival.

2. Materials and methods

From November 1994 to August 2005, a repeat mediastinoscopy was performed in 104 patients (98 men, 6 women) after induction therapy for locally advanced NSCLC; 58 procedures were performed in the Hospital Mutua de Terrassa and 46 at the University Hospital of Antwerp. Mean age was 64.3 years (range 38—85 years). All patients had proven mediastinal involvement (N2 or N3 disease) at first mediastinoscopy and were given induction or neoadjuvant therapy.
At first mediastinoscopy, the lymph nodes (LN) were classified according to the original map described by Naruke et al. [8]. The mean number of LN stations sampled was 5 (station 2 bilateral, station 4 bilateral and station 7). The mean number of LN sampled at each station was 2. At repeat mediastinoscopy, we especially examined the LN stations that were found positive at the first mediastinoscopy but also the other stations, if this was feasible. Regarding histology, 38 patients had adenocarcinoma, 40 patients squamous cell carcinoma and 26 patients large cell carcinoma. Neoadjuvant cisplatin-based chemotherapy was given in 79 patients and chemoradiotherapy in 25. Regarding radiotherapy, 45 Gy were given to the primary tumour and involved mediastinal nodes. Follow-up data were completed in January 2007; so, minimum follow-up for surviving patients was 18 months. Survival analysis was performed by the Kaplan—Meier method. By uni- and multivariate analysis, according to the Cox regression model, significant prognostic factors in relation to survival were determined. A \( p \) value less than 0.05 was considered significant.

3. Results

Remediastinoscopy was technically feasible in all patients. One patient died during the intervention due to haemorrhage from an atherosclerotic plaque at the origin of the brachiocephalic trunk, complicated with haemopericardium and cardiac arrest, giving a mortality of 1%. As morbidity, one haemorrhage from a bronchial artery was encountered which was controlled by packing; there were also one superficial wound infection, treated with drainage and antibiotics; an unintended biopsy of the right lung that was attached to the right tracheobronchial angle with no further consequences; and a puncture of the superior vena cava with the dissection cannula that required packing and right thoracotomy, during which a right pneumonectomy was performed.

Remediastinoscopy was positive in 40 patients and negative in 64. Thus, the latter group was clinically downstaged to ycN0 or ycN1 and these patients underwent lung resection. The former group received radiotherapy or combined chemoradiotherapy. During thoracotomy, a systematic nodal dissection was performed. There were 47 true-negative outcomes (RO resection) and 17 false-negative mediastinoscopies (microscopic residual disease), giving a diagnostic sensitivity, specificity and accuracy of remediastinoscopy of 71%, 100% and 84%, respectively. In the false-negative group, micrometastases were discovered after definitive pathological examination in the subcardinal (station 7) and tracheobronchial (station 4) nodes. The patients with false-negative outcomes received postoperative radiotherapy. Remediastinoscopy was negative in the other four patients, who underwent thoracotomy. In three patients no residual nodal disease was found, but in the other, definitive pathologic analysis revealed metastatic disease in a single node of the left scalene fat pad.

We also determined the diagnostic value of the procedure, according to the type of induction treatment. In patients who had neoadjuvant chemotherapy (\( n = 79 \)), sensitivity, specificity and accuracy of repeat mediastinoscopy was 71%, 100% and 82%, respectively; whereas for patients who received induction chemoradiotherapy (\( n = 25 \)), the results were 63%, 100% and 88%, respectively.

Follow-up was complete in all patients. During follow-up 69 patients died, mostly of distant metastases. Causes of death were: local recurrence in 5 patients, distant metastases in 21 patients, combined local recurrence and distant relapse in 11 patients, unrelated causes (cardiac arrest, cerebrovascular attack) in 19 patients and unknown in 13 patients. Median survival time for the whole group was 18 months (95% confidence interval [CI] 11—25). Median survival time in patients with a positive remediastinoscopy was 14 months (95% CI 8—20), with a negative remediastinoscopy 28 months (95% CI 15—41), and with a false-negative remediastinoscopy 24 months (95% CI 3—45) [Table 1, Fig. 1]. In univariate analysis, the difference between positive and negative remediastinoscopies was highly significant (\( p = 0.001 \)). In the combined group of patients with positive and false-negative remediastinoscopies (\( n = 57 \)), median survival time was 15 months (95% CI 9—21) [Table 1, Fig. 2]. In univariate analysis, the difference with negative remediastinoscopy remained significant (\( p = 0.007 \)). In a forward stepwise multivariate analysis, including sex, age, histology, centre, and nodal status at repeat mediastinoscopy, only nodal status was a significant independent prognostic factor (\( p = 0.008 \)). Relative risk of death in patients with positive remediastinoscopy was 1.99 (95% CI 1.2—3.3).

4. Discussion

Since the accuracy of non-invasive procedures like computed tomography and magnetic resonance is too low to determine a precise response after induction therapy, interest in other restaging procedures has been growing [4,9,10]. PET scanning does not reliably predict pathologic response to preoperative chemotherapy in NSCLC in either the primary tumour or the draining lymph nodes [11—14]. Port et al. reported, in a prospective study including 25

<table>
<thead>
<tr>
<th>Patient group</th>
<th>( N )</th>
<th>Histology(^a)</th>
<th>MST (95% CI)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True-positive</td>
<td>40</td>
<td>Sq cell ca: 11</td>
<td>Adenoca: 19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Large cell ca:</td>
<td>10</td>
</tr>
<tr>
<td>False-negative</td>
<td>47</td>
<td>Sq cell ca: 18</td>
<td>Adenoca: 17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Large cell ca:</td>
<td>12</td>
</tr>
<tr>
<td>False-negative</td>
<td>17</td>
<td>Sq cell ca: 11</td>
<td>Adenoca: 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Large cell ca:</td>
<td>4</td>
</tr>
<tr>
<td>Combined true-positive +</td>
<td>57</td>
<td>Sq cell ca: 22</td>
<td>Adenoca: 21</td>
</tr>
<tr>
<td>false-negative</td>
<td></td>
<td>Large cell ca:</td>
<td>14</td>
</tr>
</tbody>
</table>

\(^a\) Sq cell ca: squamous cell carcinoma; Adenoca: adenocarcinoma; Large cell ca: large cell carcinoma.
\(^b\) MST: median survival time (months); CI: confidence interval.
patients with NSCLC treated by induction chemotherapy, a positive predictive value of PET to detect persisting nodal disease of 73%, but less than 20% for residual N2 disease [13]. On the other hand, integrated PET-CT, combining anatomical and functional information has shown to be more promising [15].

We report a mortality and morbidity rate of 1% and 2%, respectively. Several other minimally invasive techniques for restaging the mediastinum have shown to be promising but they only provide cytological proof of mediastinal involvement. These include endoscopic oesophageal and endobronchial ultrasound (EEUS and EBUS) and transbronchial needle aspiration (TBNA). Although high false-negative rates (between 20 and 30%) have been reported, accuracy is similar to that of a repeat mediastinoscopy (75–83%) [16–18]. A more detailed description is provided in a recent review paper [25]. These minimally invasive techniques can be used to obtain an initial cytological proof of mediastinal nodal involvement. After induction therapy the mediastinum can be restaged by mediastinoscopy. In this way a technically more demanding mediastinoscopy is avoided. Although the accuracy of a repeat mediastinoscopy is lower than that of a first mediastinoscopy, it remains a valuable restaging tool as it provides pathological proof of downstaging or persisting mediastinal involvement. Results of this retrospective study are in accordance with the previously published results of the diagnostic value of mediastinoscopy [3,5,6]. In the present study, median survival time of patients with a positive and/or false-negative mediastinoscopy was significantly lower than those with a negative repeat mediastinoscopy. With a positive mediastinoscopy, the relative risk of dying was 1.99, compared to those patients who had a negative repeat mediastinoscopy. Thus, only those patients with a tumour downstaged to ycN0 or ycN1 after induction therapy will benefit from a lung resection. A clear association between survival and mediastinal lymph node clearance after chemotherapy in locally advanced NSCLC has been previously reported [19–22]. Betticher et al. showed that persisting N2 after induction therapy is associated with a poor prognosis [23]. Albain et al. reported a 5-year overall survival after induction chemoradiotherapy and surgery of 41% if ypN0 at surgery, 24% if ypN1–3 and 8% when no surgical resection was performed [22].

There are few other reports in literature specifically studying survival after mediastinoscopy [1,7,24]. In a preliminary study, 5-year survival rate for patients with ypN0 (n = 12) was 20% in contrast to 0% for patients with ycN2 or ypN2 after mediastinoscopy (n = 24). This difference was not significant, probably due to the low number of patients with long-term follow-up. Stamatis et al. reported a 5-year survival rate for persisting N2 of 5%. Our previously reported article showed a median survival time of 41 and 7 months when respectively a negative and positive mediastinoscopy was encountered, giving a highly significant difference (p = 0.003). In the present series with a minimum follow-up of 18 months for surviving patients, the difference between positive and negative mediastinoscopies remained highly significant (p = 0.001). Considering age, sex, histology, centre, and nodal status at repeat mediastinoscopy, only nodal status was a significant independent prognostic factor for survival in our study. Pathologic findings at repeat mediastinoscopy not only determine prognosis but also select those patients who will benefit from a subsequent thoracotomy.

In conclusion, although one fatal case was encountered, this larger series study confirms that mediastinoscopy remains a valuable restaging procedure after induction therapy in patients with NSCLC. Prognosis is poor in patients with persisting mediastinal nodal involvement. In this way, futile thoracotomies are avoided.

References


Appendix A. Conference discussion

Dr P. De Leyn (Leuven, Belgium): Regarding morbidity and mortality, one patient died, one patient had a bleeding package and then a pneumonectomy. What do you think about the mortality and morbidity of this restaging method when you know that about 60% of your patients still have persistent N2 disease with a very dismal survival? Morbidity and mortality seem for me quite high. Could you focus a little bit on other restaging techniques which might not be so invasive.

When we look at the time period, 100 mediastinoscopies were performed in a period of about 10 years. On average there were 10 re mediastinoscopies in two dedicated centres per year. I guess that more patients had induction treatment in these two centres. So how were patients selected for mediastinoscopy? Was this some indication bias?

And then my last question, it might be that the accuracy and the difficulties of mediastinoscopy are related due to the previous mediastinoscopy. Can you give us an idea how many lymph node stations were routinely sampled at the first mediastinoscopy?

Dr De Waele: To begin with the last question, normally a random selection of four nodes were sampled, so station 3, station 4 and subcarinal station No. 7.

And as far as repeat mediastinoscopy, we tried to go back to the same stations.

As for the first question, we only encountered one fatal case. It was due to a haemorrhage from plaque at the origin of the brachiocephalic trunk.

As for the morbidity, we encountered one superficial wound infection. We also did an unintended biopsy of the right lung because it was very closely adhered to the tracheobronchial angle. We also encountered bleeding from the superior vena cava, and that was controlled by packing and further on with a pneumonectomy.

And as for non-invasive staging procedures, PET doesn’t reliably predict pathologic response to preoperative chemotherapy in non-small cell lung cancer in either the primary tumour or the draining lymph nodes. Other procedures like PET-CT are still under investigation.

Dr De Leyn: Or fine-needle aspiration.

Dr De Waele: As well as fine-needle aspiration. I think we have limited data on that as far as restaging procedures after induction therapy. For PET-CT I think also at this moment it is not very significant.

Dr De Leyn: There were approximately 10 re mediastinoscopies per year, I can imagine that more patients in these centres get induction chemotherapy. How were patients selected for mediastinoscopy, or were there only 10 patients who got induction chemo?

Dr De Waele: Well, we performed a selection. Only those patients who had initially N2 or N3 stage status were included in our series. The other ones who had a lack of follow-up or that only received chemo or chemoradiotherapy were excluded. We didn’t have N2 or N3.

Dr De Leyn: But all patients who had induction chemo/chemoradio for N2, N3 with response or stable disease underwent mediastinoscopy. Is it correct?

Dr De Waele: Perhaps Professor van Schil will answer that.

Dr van Schil: No, this is not correct, because quite a lot of patients participated in a protocol of induction therapy, for example, the EORTC 08941 trial, and in that trial it was specifically stated that restaging was only done by CT scan and not by repeat mediastinoscopy which was even not allowed.

The patients presented here were treated outside a specific protocol or refused to participate, for example, in the EORTC trial. So in fact, those were selected patients.

Dr A. Oliaro (Torino, Italy): You have reported the bleeding. The bleeding is the most important problem in mediastinoscopy. You reported one pneumonectomy. I think one should offer innominate artery.

Dr De Waele: The pneumonectomy was performed by Dr Rami-Porta. If I recall it was done by thoracotomy but I’m not sure.
Dr Oliaro: And you have the bleeding from the mediastinoscopy, you perform a thoracotomy not a median sternotomy?

Dr De Waele: Since this event occurred in the centre of Dr Rami-Porta, perhaps he could comment on that.

Dr Rami-Porta: We have the doubtful privilege to have the first intraoperative death in mediastinoscopy. And what we did was a median sternotomy.

I would like to stress that we should not blame the technique, we should blame the surgeons. We indicated very poorly that intervention. The patient was elderly, had a history of cardiovascular disease, and probably we didn’t pay attention to the radiographic images and that patient had plaques in the aortic arch and the origin of the innominate artery which we found when we reviewed all the material. That patient should have never entered an induction protocol.

We, in our practice, have been very unselective in induction therapy. We have introduced patients with multiple level N2 disease, because in our experience the bulk of the tumour before induction is not predictive of response, so we have given the chance to all these patients to have a response. And if at remediastinoscopy there was no nodal disease, then they have experienced the bulk of the tumour before induction is not predictive of response, so we have given the chance to all these patients to have a response.

And if at remediastinoscopy there was no nodal disease, then they have undergone thoracotomy. And what we did was a median sternotomy.

But as I said, this was a very bad indication. This patient should have never been included in an induction therapy protocol.

Dr E. Rendina (Rome, Italy): Well, what Dr Rami-Porta has just said is an example of intellectual honesty, I think. We should all appreciate that.

I have two very small questions. We have a limited experience with mediastinoscopy and we noticed that there is a marked difference if the patient had only chemotherapy or chemoradiotherapy. Could you comment on that? This is the first point.

The second point; this experience of yours covers the years from ’94 to 2006. Now, technology has evolved over this period; don’t you think that an approach including PET scan as the first line of staging before induction therapy and eventually mediastinoscopy after induction chemotherapy would be more appropriate than a first mediastinoscopy up front and then a mediastinoscopy after induction?

Dr De Waele: I think for the last question, PET scan and PET-CT is helpful too, but as a mediastinoscopy still offers us pathologic proof, I do think we can first obtain a mediastinoscopy. After induction therapy, we would still perform a repeat mediastinoscopy.

Dr Rendina: So your current attitude is still to perform mediastinoscopy twice?

Dr De Waele: Yes. And the first question, could you repeat it?

Dr Rendina: Are there technical differences in the difficulty if the patient had only chemotherapy or chemoradiotherapy?

Dr De Waele: When a patient has received radiotherapy, more fibrosis is encountered, so it’s more difficult to obtain a good sampling of the lymph nodes. But we didn’t make a differentiation in this study. There were 79 patients who received chemotherapy and the other ones received chemoradiotherapy.

Dr T. Dosios (Athens, Greece): I have also two questions. The first is that I understood that some of your patients were found to have N3 disease in the initial evaluation. And some of them were found to be N3-negative in the second mediastinoscopy, in the repeat mediastinoscopy. Do you think that these patients who have N3 disease in initial estimation should be operated on? This is the first question.

And the second is, how many days after the last radiotherapy did you perform the mediastinoscopy?

Dr De Waele: We encountered six patients who were initially N3-positive. Two of them had a positive mediastinoscopy so underwent chemo or chemoradiotherapy. Four of them were negative. In three of them, no residual disease were found; and in only one patient, a single node of the left scalene patch was found positive. So I do think, in N3 patients, it’s possible to perform a thoracotomy or repeat mediastinoscopy.

Dr Van Schil: I have also two questions. The first is that I understood that some of your patients were found to have N3 disease in the initial evaluation. And some of them were found to be N3-negative in the second mediastinoscopy, in the repeat mediastinoscopy. Do you think that these patients who have N3 disease in initial estimation should be operated on? This is the first question.

And the second is, how many days after the last radiotherapy did you perform the mediastinoscopy?

Dr De Waele: That, I don’t know.

Dr H. Li (Shanghai, China): Actually from your conclusions that the pathologic findings on repeated mediastinoscopy can predict prognosis, I do agree with this. But for the second one that it can be used for selection of patients for lung resection after induction therapy, I think you might mean after induction therapy for the N2 disease is not indicated for lung resection. But in your study you didn’t randomise the patients, I mean, for the patients after induction therapy, for the N2 patients, you didn’t randomise them into two groups, one for surgery and the other no surgery.

So I think for these groups of patients, induction therapy for these patients is not sensitive. Maybe surgery has some role in this group of patients. So what do you think about this?

Dr De Waele: If you have N2 status after repeat mediastinoscopy, we wouldn’t perform a thoracotomy, so only radiotherapy would be given. If you’re negative, then we would perform a thoracotomy.

Dr P. Dartevelle (Le Plessis Robinson, France): How many mediastinoscopies do you perform a year compared to the number of patients you resect for non-small cell lung cancer? How many, approximately?

Dr De Waele: I don’t know precisely.

Dr van Schil: Just a remark on the radiotherapy. We try to do the repeat mediastinoscopy within 4 weeks after the end of radiotherapy. In our centre we perform approximately 80–100 routine cervical mediastinoscopies a year.

Dr De Waele: I think for these groups of patients, induction therapy for these patients is not sensitive. Maybe surgery has some role in this group of patients. So what do you think about this?