Role of cervical mediastinoscopy in staging of non-small cell lung cancer without enlarged mediastinal lymph nodes on CT scan

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Abstract

Objective: The results of primary surgery for non-small cell lung cancer (NSCLC) with involved ipsilateral mediastinal or subcarinal lymph nodes (N2 disease) remains poor. However, several studies suggest that induction chemotherapy could increase long-term survival in patients with N2 disease. Therefore, accurate preoperative staging of the mediastinum remains of paramount importance for the treatment policy in patients with NSCLC. Enlarged mediastinal lymph nodes (MLN) on CT scan are positive in only half of the patients. Small lymph nodes can contain metastatic deposits of clinical importance. However, many surgeons believe that a normal mediastinum at computed tomography allows them to cancel their preoperative mediastinal exploration. It was the aim of this study to evaluate the results of cervical mediastinoscopy in patients without enlarged MLN on CT scan.

Methods: Between January 1990 and June 1994, 235 patients with potentially operable NSCLC underwent a cervical mediastinoscopy despite the absence of enlarged MLN on CT scan. MLN were considered enlarged if they were equal to or larger than 15 mm at their maximal cross-sectional diameter.

Results: Cervical mediastinoscopy was positive in 47 patients (20%). In 21 patients, N2 disease was extranodal and in 16 patients more than one level was involved. Mediastinoscopy was positive in 9.5% of the cT1NO cases, in 17.7% of the cT2NO lesions, in 31.2 and 33.3% of cT3NO or cT4NO tumors, respectively. After a negative cervical mediastinoscopy, resectability for unforeseen N2 disease was as high as 95%.

Conclusion: We recommend a cervical mediastinoscopy in every patient with potentially operable NSCLC. © 1997 Elsevier Science B.V.

Keywords: Mediastinoscopy; N2 disease; Specificity; Carcinoma, non-small cell lung; Lung surgery

1. Introduction

Survival and therapy of non-small cell lung cancer (NSCLC) largely depends on the stage of the disease [16]. Involvement of mediastinal lymph nodes (MLN) is a very negative prognostic factor for both the resectability rate and the long-term survival. Because of this, cervical mediastinoscopy has an important role in staging of NSCLC [24]. Patients with involved ipsilateral mediastinal or subcarinal lymph nodes (N2 disease), diagnosed at the time of cervical mediastinoscopy have a low complete resectability rate and a 5-year survival of only 9% [18]. This explains why this diagnostic tool was used in many centers in Europe and North America [19].

In the 1980s however, computed tomography (CT) has been introduced and used as a non-invasive method for staging of the mediastinum. We are all aware of the fact that enlarged nodes on CT scan are only positive in half of the patients [7]. Although small lymph nodes may contain metastatic deposits of clinical importance,
many surgeons use CT scan as their selection criteria to perform cervical mediastinoscopy in patients with NSCLC. This attitude was also based on the idea that no alternative was available for these patients and they should benefit from exploration and if possible, from complete resection. Recently, many retrospective and two small randomized trials showed that induction chemotherapy seems to increase both resectability and 5-year survival in patients with N2 disease [2,14,20,21]. Furthermore, we have shown in a previous study [6] that the complete resectability rate in patients with a negative cervical mediastinoscopy and involved MLN diagnosed peroperatively (unforeseen N2 disease) was higher than in cN0 patients who had not undergone invasive preoperative staging of the mediastinum.

In the present retrospective study, we analyzed the value of cervical mediastinoscopy in the staging of 235 patients with NSCLC in the absence of enlarged MLN on CT scan.

2. Patients and methods

Between January 1990 and June 1994, 355 consecutive patients with potentially operable NSCLC and no enlarged MLN on CT scan were treated in our departments. Patients were staged by means of clinical examination, biochemical analysis (alkaline phosphatase, liver enzymes, Carcino Embryogenic Antigen), chest X-ray, chest CT scan, bronchoscopy, ultrasound of the abdomen completed by upper abdominal CT-scan in case of equivocal findings. A bone scan was performed in case of bone symptoms or disturbed biochemical results. A CT scan of the brain was done in case of neurological signs and in all patients with adenocarcinoma. When cytology or bronchoscopic biopsy failed to give a histological diagnosis, no transthoracic needle biopsy or aspiration was done.

Computed tomography of the chest was done in all patients. Contiguous 8 mm thick sections were obtained with a third generation scanner (Siemens DR Somaton or General Electric 9800) extending from the pulmonary apices to the adrenal glands. In the region of the lung hili 5 mm thick sections were scanned. A power injection was used to perform a bolus injection of 2 ml/s of contrast medium during 40 s. Scan delay was 40 s. All scans were thoroughly reviewed by the same chest radiologist (J.V.) and discussed at a multidisciplinary preoperative conference of chest physicians, radiologists and thoracic surgeons. MLN were considered enlarged if they were equal to or larger than 15 mm at their maximal cross-sectional diameter.

A total of 355 patients had no enlarged lymph nodes on CT scan (N0 disease). Patients with a preoperative histology of small cell carcinoma (n = 7) were excluded. The flow diagram of surgical procedures in these 355 patients is shown in Fig. 1.

In the study period we did not perform cervical mediastinoscopy in patients with squamous cell carcinoma and radiological T1N0 or T2N0 tumors. This was based on a large retrospective study (569 patients) from our center [7]. This study has shown that, in this group of patients the rate of unforeseen N2 disease was as low as 16%. At that time, primary surgery was the only option for patients with N2 disease. Nowadays, chemotherapy prior to local treatment seems the most valid treatment option for patients with N2 disease. A total of 120 patients with preoperative staging of T1N0 or T2N0 squamous cell carcinoma underwent straight thoracotomy without mediastinoscopy. An exception was made for 24 patients with T1N0 or T2N0 squamous cell carcinoma. In these patients, a cervical mediastinoscopy was performed because of patient related risk factors. In 211 patients histology was ether unknown or different from squamous cell carcinoma.
Cervical mediastinoscopy was performed in the same operative session with frozen section of the MLN. During cervical mediastinoscopy, upper right and left paratracheal nodes (position 2), precarinal lymph nodes (position 3), lower right and left paratracheal nodes (position 4) and subcarinal nodes (position 7) were dissected and biopsied. Lymph node classification was adapted from Naruke [16]. This procedure was performed very precisely and was always done (or assisted) by a consultant thoracic surgeon. When mediastinoscopy was negative, exploration with intention to perform complete resection was done in all these patients. At subsequent thoracotomy, sampling of MLN with frozen section was performed. If MLN proved to be positive, a radical lymphadenectomy was performed.

3. Results

Fig. 2A and B show the pre- and postoperative histology in the 235 patients with NSCLC in which a cervical mediastinoscopy was done despite the absence of enlarged MLN on CT scan. In most of these patients (97 or 41.3%) the histological type was unknown preoperatively. The preoperative histology showed squamous cell carcinoma in 71 patients, large cell carcinoma in 41 patients, adenocarcinoma in 23, adenosquamous carcinoma in 2 and bronchioloalveolar carcinoma (BAC) in 1 patient. Histology of the resection specimen proved to be squamous cell carcinoma in 119 patients, adenocarcinoma in 65 patients, large cell undifferentiated carcinoma in 25, small cell carcinoma in 12, adenosquamous cell carcinoma in 8 and BAC in 6. Most patients in this study had a T2N0M0 lesion (130 or 55.3%). A T1N0 lesion was found in 42 patients, a T3N0 and T4N0 in 48 and 15 patients, respectively. In 47 patients (20%), the cervical mediastinoscopy was positive. In 16 patients (34%) more than one level was involved and in 45% of the patients (n = 21) the N2 disease was extranodal. Fig. 3 shows the prevalence of positive mediastinoscopy according to the postoperative histology. The mediastinoscopy was positive in 16.8% of patients with squamous cell carcinoma whereas it was positive in 21.5% of those with adenocarcinoma (P > 0.05). For large cell carcinoma and small cell carcinoma, the mediastinoscopy was positive in 36 and 33% of the cases, respectively.

Fig. 4 shows the prevalence of a positive mediastinoscopy according to the clinical T stage of the tumor. For T3NO and T4NO lesions, the cervical mediastinoscopy was positive in 31.2 and 33.3% of the cases, respectively.

3.1. T1N0 lesions

There were 42 patients who presented with a T1N0 lesion. Cervical mediastinoscopy was positive in 9.5% of these patients. Looking at the postoperative histology, the prevalence of a positive mediastinoscopy in T1N0 adenocarcinoma was 21.4%, whereas none of the 19 patients with T1N0 squamous cell carcinoma had a positive finding at cervical mediastinoscopy (P < 0.05).

3.2. T2N0 lesions

The overall incidence of a positive mediastinoscopy in this group of patients was 17.7%. Regarding the postoperative histology, 12.9% of squamous cell carcinomas, 22.2% of adenocarcinomas and 33.3% of large cell carcinomas had positive MLN (P > 0.05).

Of the 47 patients, 44 with a positive mediastinoscopy were excluded for surgery. They received radiotherapy, when palliation was indicated; 3 patients with squamous cell carcinoma were selected for surgery, because they had only one positive level without extranodal extension at mediastinoscopy.
When the mediastinoscopy was negative, we proceeded with thoracotomy \((n = 188)\). Despite this very rigorous staging of the mediastinum by means of CT scan and cervical mediastinoscopy, intraoperative staging at the time of thoracotomy showed involved MLN (unforeseen N2 disease) in 20 patients (10.6%). In 19 of these 20 patients (95%), a complete resection (R0 situation) could be achieved. The overall complete resection rate for these 188 patients was 96.8%.

4. Discussion

Staging of the mediastinum is of paramount importance in NSCLC since survival is very much determined by the status of mediastinal nodes. Pearson et al. [18] reported on 79 patients which were operated with mediastinoscopy proven positive nodes. This 79 patients were a highly selected subset of patients: patients with extracapsular spread or involvement of high paratracheal nodes were excluded for surgery. The complete resectability rate was 64% and the overall 5-year survival was only 9%. One can assume that, if thoracotomy was undertaken in all patients having positive mediastinoscopy findings, the 5-year survival would have been extremely low. A more recent study from Funatsu et al. [8] confirms this finding. They operated on 117 patients with a positive mediastinoscopy. In 26 patients (22.2%) no resection could be performed. Curative resection was possible in only 13 patients (11.1%), whereas in 78 patients (66.7%) the resection was not curative. The 5-year survival of the 92 resected patients (excluding the 26 exploratory thoracotomies) was only 6%. When the morbidity and mortality of the surgical procedure approaches the estimated 5-year survival, one has to be anxious to recommend a surgical approach for these patients.

In experienced hands, cervical mediastinoscopy has no mortality and a morbidity as low as 2.3% [12]. With cervical mediastinoscopy, not only ipsilateral, but also contralateral (N3) disease can be diagnosed. One wonders why there is still so much controversy and discussion about the use of cervical mediastinoscopy in staging of NSCLC.

A very important reason could be that many surgeons reported 5-year survival rates up to 30% after radical systematic lymphadenectomy for N2 disease [6,11,13,15,17,22,26]. However, these studies dealt with patients who either did not undergo mediastinoscopy because MLN were small on CT scan or because the mediastinoscopy was negative. Involvement of mediastinal nodes was discovered at the time of thoracotomy or at microscopic examination of resected nodes. These cases can be classified as unforeseen N2 disease [23]. Many authors (including ourselves) reported similar 5-year survival rates for these patients. This certainly does not mean that, if one performs resection in every patient with mediastinoscopy proven N2 disease, similar results will be obtained. The previously mentioned study of Funatsu et al. [8] may well illustrate this. Furthermore, we showed that the resectability rate of unforeseen N2 disease was higher in patients with a negative cervical mediastinoscopy, compared with those, who had no enlarged MLN on CT scan but did not undergo mediastinoscopy [6].

A second reason why cervical mediastinoscopy was abandoned by some groups was the introduction of CT scan for staging of MLN. Nowadays, it is well known that a positive CT result predicts actual metastatic involvement in only about half of the patients and that these patients should undergo mediastinoscopy to prove microscopic nodal involvement [7]. Although one can assume that small nodes may contain microscopic
tumor deposits of clinical importance, a negative CT result is generally accepted as proof of absence of M LN involvement. It is generally accepted that the false negative ratio of CT scan in T1N0 or T2N0 lesions is very low, and that one can proceed with thoracotomy without mediastinoscopy. For T1 and T2 lesions, as far as we know, there are no large series analyzing the value of cervical mediastinoscopy in the absence of enlarged mediastinal nodes on CT scan. A study by Goldstraw et al. [10] evaluated 13 patients with normal mediastinum and hilum on CT scan. Mediastinoscopy in all these cases was negative. He concluded that the finding of a normal mediastinum on preoperative computed tomography allows the surgeon not to perform a preoperative mediastinal surgical exploration.

Our policy was to perform a cervical mediastinoscopy even in the absence of enlarged M LN on CT scan. An exception was made for T1N0 or T2N0 squamous cell carcinomas. In 235 patients a cervical mediastinoscopy was performed and, although the nodes were not enlarged on CT scan, metastatic M LN were found in 47 patients (20%).

Overall, we found no significant difference in the occurrence of positive mediastinoscopy between squamous cell carcinoma (16.8%) and adenocarcinoma (21.5%), but a significantly higher incidence in case of large cell carcinoma. Cybulsky et al. [4] studied 124 NSCLC patients with resected involved mediastinal nodes. CT scan was negative in 61 patients. The patients in whom the CT scan was falsely negative most commonly had a histological diagnosis of adenocarcinoma.

For T1 lesions the mediastinoscopy was positive in 9.5%. This correlates with older studies (before the use of CT scan). T1 lesions without evidence of hilar or mediastinal lymphadenopathies on chest X-ray had positive mediastinoscopy findings in 14.3% [25]. Funatsu et al. [9] and Coughlin et al. [3] mention positive nodes at mediastinoscopy in 9 and 14.9% of T1 lesions respectively. Unfortunately, in their study there is no correlation with CT scan findings. The prevalence of positive mediastinoscopy was significantly higher for patients with adenocarcinoma when compared with squamous cell carcinoma. None of 19 T1 squamous cell carcinoma had a positive mediastinoscopy, whereas in a T1 adenocarcinoma mediastinoscopy was positive in 21.4%.

T2N0 lesions had a positive mediastinoscopy in 17.7%. In this subgroup no difference was found between squamous cell carcinoma and adenocarcinoma.

For T3 and T4 lesions, the false negative rate was 31% and 33%, respectively. This is in agreement with other data from the literature. Daly et al. [5] performed mediastinal lymph node dissection in patients with central T3 lesions with negative findings on CT. In 28% involved mediastinal nodes were found. Without any discussion, mediastinoscopy should be performed for every T3N0 and T4N0 lesion.

The preoperative histology was unknown in 41.3% in our series. This high figure may be explained by the fact that we do not perform transthoracic fine needle aspiration in patients with high clinical suspicion of operable NSCLC.

Despite a negative CT scan and negative mediastinoscopy, in 20 patients (10.7%) involved mediasti-
nul lymph nodes were found at the time of thoracotomy (unforeseen N2 disease). In 19 of these 20 patients (95%) complete resection with radical lymphadenectomy could be performed. A 5-year survival of 25–30% for this group can be expected. We believe that the high resectability rate is related to the systematic use of cervical mediastinoscopy [6]. To justify if mediastinoscopy is also indicated in patients with T1N0 or T2N0 squamous cell carcinoma (a group in which we did not perform cervical mediastinoscopy routinely) we looked at the 120 patients who were operated without previous mediastinoscopy. N2 disease was detected at thoracotomy in 17 patients. Only in 6 patients with unforeseen N2 disease a complete resection was possible (35%). In another 6 patients no resection could be performed because of bulky N2 disease and in 5 patients the resection was judged incomplete. This figure is worse than the overall complete resectability rate which was found in the group of patients which underwent thoracotomy after negative mediastinoscopy and further stresses our new policy to perform cervical mediastinoscopy in every patient.

This study highlights that, even with new generation CT scanners, the false negative ratio of CT in evaluating small mediastinal nodes is as high as 20%. Furthermore, a large interobserver variability in determining nodal status in NSCLC with CT scan has been described [1]. We state that, even in the absence of enlarged MLN on CT scan, a cervical mediastinoscopy is indicated. In these patients, mediastinoscopy discloses a different tumor stage in 20% of patients.

More recently, we introduced video-assisted mediastinoscopy. Enhanced visualization allows complete removal of lymph nodes (e.g. subcarinal nodes) with the use of microscissors. This may lead to better histological appreciation of intra-versus extranodal disease. With direct and simultaneous videorecording on a TV monitor several people can follow the procedure and this offers teaching capabilities. Furthermore, international use of videotaped mediastinoscopy may lead to better standardization of this procedure.

One can discuss on the best treatment for these patients with positive mediastinoscopy and small nodes on CT scan. We are reluctant to perform surgery in patients with mediastinoscopy proven N2 disease [6]. The group of Toronto [18] operated on only 20.9% of patients with positive mediastinoscopy findings. In our study, only 3 out of the 47 patients underwent surgical exploration and resection. It could be that patients with a positive mediastinoscopy but small nodes on CT represent a subgroup of N2 disease with a different prognosis from patients with enlarged nodes on CT scan. This was suggested by the study of Cybulski et al. [4]. The 5-year survival of patients with resected N2 disease was 6.6% when there was computed tomographic evidence of mediastinal lymph node enlarge-

References

Appendix A. Conference discussion

Dr Al-Kattan (Riyadh, Saudi Arabia): I want to ask two questions. I enjoyed your presentation. I want to know, first, how many false negative mediastinoscopies did you have after you went ahead with the resection? And the other question is, if you have a left upper lobe tumor, would you still go for anterior mediastinoscopy in addition to your mediastinoscopy, or are you just proposing one simple technique, which is mediastinoscopy, for more accurate staging?

Dr De Leyn: Thank you for the questions. After a negative mediastinoscopy, 10% of the patients in this series showed involved mediastinal nodes at thoracotomy. So the rate of unforeseen N2 disease was 10%. Mostly these nodes were not within the reach of the mediastinoscope like the posterior subcarinal nodes and the paraesophageal nodes. The survival after resection of unforeseen N2 disease is +25%.

To answer your second question, we perform in every patient with potential operable lung cancer a cervical mediastinoscopy, and surely in patients with left upper lobe tumors, to exclude contralateral disease. If CT scan shows no enlarged nodes in the aortopulmonary window, we don’t do a left anterior mediastinotomy. We, as others, obtain a 5-year survival of more than 30% after resection of positive nodes in this position.

Mr Thorpe (Sheffield, England): Could I just mention the Pearson technique, which is mediastinoscopy, for more accurate staging? You are just proposing one simple technique, which is mediastinoscopy, for more accurate staging?

Dr De Leyn: The Ginsberg group is doing this extended cervical mediastinoscopy with good results, but we have no experience.

Mr Odom (Manchester, England): I would certainly agree with your conclusions, having once or twice operated on patients who didn’t appear to have any nodes on CT scan but at surgery did have nodes that would have been readily accessible at mediastinoscopy. My question is about T4 tumors. Were these tumors known to be T4 before operation, and if so, why are you performing mediastinoscopies on what are, by definition, inoperable tumors?

Dr De Leyn: That’s a very good question. It is sometimes a problem to define operability in clinical T4. Sometimes we do explore patients which are on CT scan T4, because in some cases we have doubt on the clinical staging of the tumor. As we all know, a certain group of these T4 tumors proves not to be irresectable. I agree that when the patient is definite inoperable, there is no place for cervical mediastinoscopy for purposes of staging. In this study, patients were potentially operable at the onset of cervical mediastinoscopy.

Dr Dosios (Athens, Greece): How many of your patients were found at mediastinoscopy to have N3 disease?

Dr De Leyn: In this series, we only had two patients with radiological N0 disease which proved at cervical mediastinoscopy to have N3 disease. For reasons of clarity, I did not mention these figures in the slides. Out of 47 patients, only 2, that’s about 5%. However this figure may be underestimated because this is a retrospective study. This study started from 1990, a period before the use in our hospital of induction chemotherapy. At that moment, when an ipsilateral node was macroscopic positive, it was not always evident to take some risk and time to biopsy the contralateral side, since this did not influence the further therapeutic options in this patient.

Dr Dosios: Nowadays, if you have a patient with N3 disease, with just one lymph node at the contralateral side and you give the patient induction therapy, will you resect the primary tumor or not?

Dr De Leyn: At the moment we only give induction chemotherapy for stage IIIa disease. Stage IIIa includes ipsilateral disease, contralateral mediastinal disease is defined as stage IIIb disease. Patients with contralateral mediastinal disease are treated in our hospital with chemoradiotherapy.

Dr Helier: I should like to know, did you use the high resolution CT technique or not?

Dr De Leyn: Yes, in every patient a high resolution CT scan was performed. This CT scan was performed by a chest radiologist. The clinical staging of every patient was discussed on a weekly seminar of thoracic surgeons, pulmonologists, radiotherapists and chest radiologists.