Surgery for non-small cell lung cancer with unsuspected metastasis to ipsilateral mediastinal or subcarinal nodes (N2 disease)

Abstract Objective. Although the results after surgery for N2 disease are disappointing, there seems to be a subgroup of patients which may benefit from primary resection. These patients have clinically unrecognized N2 involvement that is discovered only at the time of thoracotomy (unsuspected or unforeseen N2 disease). It was the aim of this retrospective study to analyze the survival after resection for unforeseen N2 disease and to evaluate different prognostic factors. We were interested to see whether our strategy of rigorous staging of the mediastinum with mediastinoscopy or anterior mediastinotomy had an effect on the resectability rate and survival of unsuspected N2 disease.

Methods. Between 1985 and 1990, 859 patients with potentially operable non-small cell lung cancer were referred to our surgical department. Despite rigorous preoperative staging with computed tomography scan and cervical mediastinoscopy and/or anterior mediastinotomy, 103 patients (14.5%) had unsuspected N2 disease at thoracotomy. The tumor could be completely resected in 90 patients (87.5%).

Results. The 5-year survival after complete resection was 22%. Histology of the tumor, number of involved levels and extent of nodal disease had no effect on survival.

Conclusion. We conclude that resection is justified in patients with unforeseen N2 disease. Rigorous staging of the mediastinum by cervical mediastinoscopy or anterior mediastinotomy resulted in a high resectability rate and avoids unnecessary thoracotomies. Mediastinoscopy plays a central role in the staging of patients with carcinoma of the lung. [Eur J Cardio-thorac Surg (1996) 10: 649–655]

Key words Non-small-cell lung cancer · Mediastinoscopy · N2 disease · Surgical treatment

Introduction

Despite progress in medical oncology, pulmonary resection remains the most effective treatment for non-small cell lung cancer (NSCLC). However, there is controversy about the treatment of patients with locally advanced carcinoma. Most controversy exists about the management of patients with ipsilateral mediastinal lymph node metastases (N2 disease).

The vast majority of patients with N2 disease have incurable tumors [16]. Surgery for patients with “mediastinoscopy positive”, but otherwise favorable N2 disease results in an overall actuarial 5-year survival rate of 9%, and 15% for those having complete resection [12]. Martini and Flehinger [7] performed thoracotomy without prior mediastinoscopy in 179 patients who were thought to have N2 disease prior to thoracotomy. Complete resection was possible in only 32 (18%) of the patients. The 5-year survival rate for this group was only 9%. It seems that surgery for...
Table 1  Postoperative survival of patients with N2 disease (CR complete resection)

<table>
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<tr>
<th>Authors</th>
<th>Operations for unforeseen N2</th>
<th>Complete resections (%)</th>
<th>Five-year survival (%)</th>
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<tr>
<td>Martini and Flehinger (1987)</td>
<td>224</td>
<td>119 (53%)</td>
<td>30% (CR)</td>
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<tr>
<td>Naruke et al. (1988)</td>
<td>480</td>
<td>242 (50.4%)</td>
<td>19.2% (CR)</td>
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<td>Watanabe et al. (1991)</td>
<td>162</td>
<td>84 (51.8%)</td>
<td>24% (CR)</td>
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<td>Goldstraw et al. (1994)</td>
<td>149</td>
<td>127 (85.2%)</td>
<td>20% (CR)</td>
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<td>Present study</td>
<td>103</td>
<td>90 (87.4%)</td>
<td>22% (CR)</td>
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In 1985 - 1990

500 operated pN2
Resected 359 - 711 (14.5%) 90/711

859 NSCLC
819 mediastinoscopy

Fig. 1 Flow chart of surgical procedures in 859 patients with operable non-small cell lung cancer

N2 disease offers very little long-term survival. There are more and more data in the literature suggesting that surgery after induction chemotherapy results in better survival rates [1, 5, 8, 13–15].

However, a subgroup of patients with N2 disease may benefit from primary surgical resection (Table 1). This group with significant survival after resection for N2 disease comprises patients with unsuspected or unforeseen positive mediastinal lymph nodes. In these patients, N2 disease was not recognized: neither on imaging, at bronchoscopy, at mediastinoscopy nor anterior mediastinotomy, and is discovered only at thoracotomy. This retrospective study seeks to assess the incidence and effectiveness of surgery for patients with unforeseen N2 disease and to identify prognostic factors.

Material and methods

Between 1985 and 1990, 859 patients with NSCLC were considered to have operable disease according to clinical, radiologic or bronchoscopic criteria. It has been our policy to perform a cervical mediastinoscopy and/or anterior mediastinotomy in all patients except those with a T1 or T2 squamous cell carcinoma with small lymph nodes (<1.5 cm in the long axis) on computed tomography (CT) scan. The flow chart of the surgical procedures in these 859 patients is shown in Fig. 1.

In 500 patients, a mediastinoscopy was performed. In 148 patients (29.6%) the mediastinoscopy was positive. All except eight of these patients were definitely excluded for resection and received palliative radiotherapy. Three hundred fifty-two patients with negative mediastinoscopy underwent thoracotomy. Invasion of mediastinal lymph nodes was found in 46 patients (13.1%). Forty out of these 46 patients were completely resected, in six patients the tumor could not be resected. Complete resection was defined as the removal of all macroscopic tumor and lymph nodes, with clear resection margins on microscopic examination. Three hundred fifty-nine out of the 859 patients underwent a straight thoracotomy without previous mediastinoscopy. In 57 patients N2 disease was found (15.9%). Fifty patients underwent a complete resection, seven exploratory thoracotomies were performed.

Involution of mediastinal lymph nodes was found at thoracotomy in 103 patients. In 90 patients, the tumor and involved nodes could be completely resected. The resectability of the primary tumor in patients with unforeseen N2 disease was 87.4% (90/103).

At cervical mediastinoscopy, the following lymph node stations were sampled: highest mediastinal (1), upper paratracheal (2), pretracheal (3), lower paratracheal (4) and subcarinal (7). Lymph node classification nomenclature was adapted from Naruke [10]. At operation, mediastinal lymph node sampling was routinely performed in all patients. These lymph nodes were investigated by frozen section and a radical mediastinal lymph node dissection was performed whenever N2 disease was discovered at thoracotomy.

Follow-up was obtained from the medical records and by questionnaires to the referring physicians. Actuarial survival rates were calculated using the Kaplan-Meier method. The standard errors are shown in the graphs. Statistical comparisons between the slopes of the curves were calculated using the log-rank test. Operative mortality (30-day) was included in the survival analysis.

Results

As shown in Fig. 2, the actuarial 5-year survival rate after complete resection for unforeseen N2 disease (90 patients) was 22±9%. Histologic examination among the 90 patients who underwent resection for unforeseen N2 showed squamous cell carcinoma in 56 (62.2%), adenocarcinoma in 24 (26.6%), large cell undifferentiated carcinoma in 3 (3.3%) and mixed features in 7 (7.7%).

The further analysis is focused on the 56 patients with squamous cell carcinoma and 24 patients with adenocarcinoma. The mean age of these patients was 60 years (40–76). There were 76 men and 4 women. Pneumonec- tomy was performed in 63 patients, lobectomy in 17 patients. In all these patients, an extensive mediastinal lymphadenectomy was performed. The hospital mortality was 6.2% (5 patients). This is comparable with earlier reported mor-
Resected unforeseen N2 disease (n=90)

Squamous cell carcinoma (n=56)

Adenocarcinoma (n=54)

T2N2 tumors (n=47)

T3N2 tumors (n=30)

Intranodal (n=41)

Extranodal (n=30)

Fig. 2 Actuarial survival after resection for unforeseen N2 disease (n = 90)

Fig. 3 Actuarial survival after resection comparing adenocarcinoma (closed squares) with squamous cell carcinoma (open circles)

Fig. 4 Actuarial survival after resection comparing T2 (open circles) with T3 tumors (closed squares)

Fig. 5 Survival after resection comparing intranodal (open circles) versus extranodal (closed squares) unforeseen N2 disease

tality rates in our center [3]. The pT stage of these tumors was T1 in 6; T2 in 47; T3 in 33 and T4 in 7. In 41 patients the disease was intranodal, in 30 patients there was extranodal disease. In nine patients it was impossible for the pathologist to differentiate between intra- and extranodal. Metastatic disease was present in one nodal station in 53 patients, while in 27 patients more than one was involved.

The actuarial survival in these 80 patients with resection for unforeseen N2 disease was 24 ± 7%. A number of variables have been studied to assess their influence on survival following resection for N2 disease. The 5-year survival rate was the same in patients with adenocarcinoma and squamous cell carcinoma (Fig. 3, 20 ± 13% versus 26 ± 8%; P > 0.05). Survival for T2 tumors was significantly better than for T3 tumors (Fig. 4; 3-year survival of 37 ± 7% versus 5 ± 5%; P < 0.005). There were no 5-year survivors with T3N2 tumors. When the disease was intranodal, there was a trend (Fig. 5) to better survival when compared with extranodal disease (5-year survival rates of 29% and 19%, respectively), but this difference was not statistically significant. Patients with involvement of one node station had no better prognosis than patients with involvement of more than one (5-year survival 24 ± 9% versus 25 ± 11%). Table 2 shows the different parameters such as cell type, location of tumor, type of intervention, number of involved nodes, location of involved levels and extent of disease in patients surviving more than 36 months.

Discussion

In non-small cell lung cancer, surgery offers the best chance for definitive cure. The prognosis after surgical
Table 2 Characteristics of long-term survivors after complete resection for unforeseen N2 disease (Ad adenocarcinoma, Sq squamous cell carcinoma, pn pneumonectomy, slpn sleeve pneumonectomy, upbil upper bilobectomy, LUL left upper lobe, RUL right upper lobe, RLL right lower lobe, RML right middle lobe, LLL left lower lobe, RMBr right main bronchus, LMBr left main bronchus, I intranodal disease, E extranodal disease, RBrI right bronchus intermedius)

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<tr>
<th>Survival (months)</th>
<th>Cell type</th>
<th>Intervention</th>
<th>Location of tumor</th>
<th>No of involved nodes</th>
<th>Level of involved nodes</th>
<th>Extent of disease</th>
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<tr>
<td>66</td>
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treatment for non-small cell lung cancer (NSCLC) depends greatly on the extent of nodal involvement. There is much controversy regarding the surgical management of NSCLC associated with ipsilateral mediastinal or subcarinal lymph node metastasis (N2 disease). Although the 5-year survival rate for the whole group of patients with N2 disease is reported to be as low as 2% [16], long-term actuarial survival rates varying from 15% to more than 30% are frequently reported in the surgical literature (Table 1). This is probably the reason why N2 disease is widely misunderstood and why surgeons have different criteria for the use of mediastinoscopy and differ in their attitudes towards surgical treatment of N2 disease.

It must be clear that the vast majority of patients with N2 disease have non-resectable tumors and the place of surgical treatment should not be overestimated. According to Shields [16], patients with N2 disease can be divided into four categories. The first group are patients with symptomatic N2 disease such as superior vena cava syndrome and hoarseness. Despite any treatment, long-term survival, even after induction chemotherapy, is very unlikely in these patients.

The second group has no symptoms related to involved nodes, but N2 disease is grossly evident on X-ray or bronchoscopy. In a series of 706 patients with N2 disease reported by Martini and Flehinger [7], 482 patients had clinical evidence of N2 disease. Only a minor percent of these patients had undergone preoperative mediastinoscopy. Three hundred one of these patients (62%) were considered inoperable because of extensive local spread (stage IIIb) or the presence of distant metastasis (stage IV). Hundred seventy-nine patients with clinically evident N2 disease underwent exploration and only 32 patients (18%) could be completely resected. These 32 patients represent only 6% of all patients with clinical N2 disease. From this study, it is clear that primary surgery in this group of patients has little impact on prognosis. There is evidence from either retrospective or small prospective studies that induction chemotherapy can improve resectability and long-term survival in these patients [1, 5, 8, 13–15].

The third group contains patients with no evidence of disease in the mediastinum on X-ray and bronchoscopic studies, but N2 disease is discovered at the time of prethoracotomy mediastinal exploration. In most series 80–90% of such patients have non-resectable disease as the result of extracapsular extension, mediastinal fixation, unfavorable location or multiple levels of involvement. In our series, only eight out of the 148 patients (5.4%) with positive mediastinoscopy were selected for surgery. Pearson [12] reported on 79 patients who were operated on despite a positive mediastinoscopy. Fifty-one patients could be completely resected; the 5-year survival rate was only 9%.

The fourth group are patients with clinically unrecognized N2 involvement (neither radiographically, bronchoscopically nor at mediastinal exploration) that is discovered only at thoracotomy. These patients are defined to have unforeseen or unsuspected N2 disease. Unfortunately, unforeseen N2 disease is not a rare thing. Despite our efforts...
to identify N2 disease prior to thoracotomy, as many as 14% of our patients with NSCLC were found to have unsuspected N2 disease.

Patients with unforeseen N2 disease appear to have a good prognosis provided the tumor and involved nodes can be completely resected. In the literature, actuarial 5-year survival rates vary between 20% and 30% (Table 1). There is, however, a tremendous variation (50%–87%) between the different authors in the rate of complete tumor resection. In the series reported by Martini and Flehinger [7], 224 patients were thought, based on clinical staging, to have N0 or N1 disease, but N2 disease was discovered at operation. Only in 119 patients (53%) could a complete resection be performed. The 5-year survival rate of these 119 patients with completely resected N2 disease was 30%. Naruke and associates [11] performed thoracotomy in 480 patients with N2 disease without previous mediastinoscopy. Complete resection was only possible in 242 patients (50.4%). The 5-year survival rate after complete resection was 19.4%. In the series of Watanabe [19], only 51.8% of patients with N2 disease found at thoracotomy could be completely resected, with a 5-year survival rate of 24%. Martini, Naruke and Watanabe do not routinely explore the mediastinum prior to surgery as part of staging for NSCLC. We, as well as Goldstraw [6], have extended indications for mediastinoscopy or anterior mediastinotomy and this results in a high resectability rate (85% and 87%, respectively).

The 5-year survival rate did not differ according to the histology of the tumor (26% for squamous cell carcinoma versus 20% for adenocarcinoma). This finding is consistent with other reports by Martini [7], Watanabe [19], Cybulski [2] and van Klaveren [18]. However, other authors [6, 9, 10, 12, 15] noted a worse prognosis for adenocarcinoma compared to squamous cell carcinoma. Histologic typing of the entire population with proven N2 disease (148 mediastinoscopy positive and 103 unsuspected) showed the following distribution: squamous cell carcinoma: 26%, adenocarcinoma: 37%, and large cell carcinoma 56%.

From these data it is obvious that the prevalence of metastatic spread to mediastinal nodes is higher for adenocarcinoma than squamous cell carcinoma.

Unforeseen T2N2 tumors had a much better prognosis compared with T3N2 tumors (5-year survival rate of 34% versus 0%, respectively). Although this is a retrospective study and we must realize that all events are multifactorial, one can question whether resection is still justified for T3N2 tumors. Patients with intranodal disease had a slightly better survival, but the difference in survival was not statistically significant from that for patients with extracapsular spread of the disease. Similar findings were reported by Cybulski et al. [2] and van Klaveren et al. [18]. Martini and Flehinger [7] reported that single level nodal involvement resulted in better survival than multinodal level involvement. Like Goldstraw [6] and van Klaveren [18], we did not find any difference in 5-year survival rate between these two groups.

We conclude that long-term survival in patients with unforeseen N2 disease is possible, provided the tumor is completely resectable. Histologic type of the tumor, number of levels involved, extent of nodal disease and adjuvant radiotherapy did not influence survival. The resectability in patients with N2 disease discovered at thoracotomy varies with the routine use of mediastinoscopy. Furthermore, it may be important to diagnose N2 disease preoperatively, since induction chemotherapy seems to increase the resectability as well as long-term survival. However, at the present time, the benefit of induction chemotherapy is not yet proven and further randomized trials need to be awaited.

In experienced hands, mediastinoscopy and anterior mediastinotomy have no mortality and only minimal morbiditity with a sensitivity of 86% [4]. With a negative mediastinoscopy, the resectability for unforeseen N2 disease is as high as 87% and a 5-year survival rate of 24% can be expected after complete resection. For these reasons it is our and others' belief [6, 17] that mediastinoscopy remains an essential procedure in the staging of potentially operable NSCLC.

References

Dr De Leyn: It was shown in the 1980s, by resectability for patients with positive reed-the study of Pearson et al., that complete patients there are also some 15% 5-year during the operation. Maybe among those take the risk that they have positive nodes figure, and for that one-fifth of the patients, important. This might raise the question of leukemia in stage IIIa-N2 non-small cell lung cancer. Cancer 73:2589-2598


Dr. Laequet: When 20% or 20% is far from satisfying, still it is a remarkable figure, and for that one-fifth of the patients, 5-year survival or maybe longer is very impo-tent do you think this reflects inadequacy of mediastinoscopy in the staging? In the future, we could stage the mediasti-nally involved, intranodally, on the same side as the tumor and, very important, in a squa-mous cell carcinoma, not in an adenocar-cinoma.

Dr. De Leyn: It was shown in the 1980s, by the study of Pearson et al., that complete resectability for patients with positive medi-astinoscopy is about 60% and the long-term survival is only 9%. Furthermore one should remember that this operated group was a highly selected group of mediastino-scopy positive patients. Personally, I would be reluctant to operate on patients with mediastinal node involvement proved by mediastinoscopy. We need to await further studies to see if induction chemothera-py, which is still in an experimental phase, can increase the resectability and survival of these patients.

Dr. L. Lacquett (Nijmegen, The Nether-lands): I think, like our chairman, that there is a small group of patients with min-imal N2 disease, discovered at mediasti-noscopy, who can have the same postoper-a-tive survival as in your series. By minimal, we mean patients with one station in-volved, intranodally, on the same side as the tumor and, very important, in a squa-mous cell carcinoma, not in an adenocar-cinoma.

Dr. De Leyn: One hundred forty-eight of the 500 mediastinoscopies performed were positive in our series. Despite a positive mediastinoscopy we resected eight pa-tients. This is a very low percentage. When we look at the survival of these eight pa-tients, two are indeed long-term survivors. So I agree with you that a small subgroup of patients with “minimal” N2 disease may benefit from resection. However, one should be very careful with the term “mini-mal”. What is the definition of “minimal”? Furthermore not all mediastinoscopies are performed in exactly the same way and “minimal” for one surgeon may be something completely different than for another surgeon. Because of the low percentage of “minimal” N2 disease, it may be dangerous to state that patients with positive mediastino-scopy can be operated on. I think we have to wait for the results of induction therapy in patients with mediastinosco-pically proven N2 disease. On the other hand, when involved mediastinal nodes are found (unforeseen N2 disease) during thoraco-tomy, the patient will benefit if the tu-mor and nodes are completely resected, so giving you a chance of 5-year survival (22%).

Mr. D. Waller ( Birmingham, UK): When you say unforeseen N2 disease, to what ex-tent do you think this reflects inadequacy of mediastinoscopy in the staging? In the light of neoadjuvant treatment for N2 disease, what do you think about the merits of potentially better staging methods, such as video-assisted thoracoscopy? Do you think, in the future, we could stage the mediasti-nummum thoracoscopy and, if these pres-umably lower paratracheal nodes are pos-i-tive, then randomize these people to neoadju-vant therapy? Do you see this as the way forward?
Dr. De Leyn: In our study of unforeseen N2 disease, involved mediastinal nodes were mostly not within the reach of the mediastinoscope. We all know that the posterior subcarinal region and para-esophageal region cannot be reached by cervical mediastinoscopy. These nodes can easily be dissected by right thoracoscopy. The question is: how far do we have to go with our staging? Personally, I don’t think we should perform any thoracoscopy to reach these nodes, because they probably don’t have the same prognostic value of upper paratracheal nodes. This is confirmed by our studies, since the long-term survival rate for unforeseen involved nodes at this location after resection is 22% or more. However, if there is a contraindication for cervical mediastinoscopy (enlarged thyroid gland, severe kyphosis) and CT scan shows enlarged nodes, one could consider performing thoracoscopy for nodal biopsy.

Another clear indication for thoracoscopy is the suspicion of malignant pleural effusion, to exclude or prove pleural tumor deposits.

Dr. T. Dosios (Athens, Greece): I am surprised to hear that probably the mediastinum or the mediastinal lymph nodes could be better investigated through thoracoscopy than through mediastinoscopy. I think that mediastinal lymph nodes can be investigated better through mediastinoscopy. I don’t know what the opinion of the audience is on that subject.

Dr. De Leyn: I fully agree with you that, for the upper mediastinum, mediastinoscopy is better than thoracoscopy. The morbidity of cervical mediastinoscopy is very low and it also has the advantage that contralateral mediastinal disease (N3 disease) can be diagnosed or excluded. We usually dissect the subcarinal nodes with visualization of the esophagus. This procedure has recently been facilitated by the use of video-assisted mediastinoscopy. However, we have to admit that posterior, deep subcarinal nodes and para-esophageal nodes cannot be reached by mediastinoscopy and these nodes can be quite easily dissected by thoracoscopy. But one again, the prognostic impact of these “lower” mediastinal nodes is different from upper mediastinal nodes and I don’t think that thoracoscopy can replace cervical mediastinoscopy for the staging of NSCLC.

Dr. W. Walker (Edinburgh, U.K.): I would just like to make two points, one in support of your concept of mediastinoscopy for all the patients, and that is that we have shown quite conclusively that node size does not correlate with malignancy. So the use of the CT scan as a determinant really isn’t very logical. A small node is just as likely to be malignant as a large node. But also in support of thoracoscopy, I would like to point out that part of the selection process has to be avoiding an open and shut thoracotomy on the irresectable N2 disease, and that may often be from local factors, which can be identified at thoracoscopy, before putting the patient through an open thoracotomy to find this out.

Dr. De Leyn: But does this mean that we have to do a thoracoscopy for nodal staging in every patient with lung cancer? When the cervical mediastinoscopy is negative and involved lower mediastinal nodes are found, the complete resectability rate in our study was as high as 87% with a 5-year survival rate of 22%. A cervical mediastinoscopy has a very low morbidity and takes about 15 min. With the use of frozen section, it can be easily performed just prior to thoracotomy. If we have to do a thoracoscopy in every patient.

Dr. Walker: No, I’m not suggesting that. I’m suggesting that if you have done a mediastinoscopy and identified this one as a target patient whom you are going to go for resection on, then I don’t think it takes you more than a few minutes to put a thoracoscope in at the beginning of the procedure and make sure you don’t have tumor flowing off the back of the hilum onto the aorta — or some other relatively simple-to-identify exclusion to resection. To put someone through an open and shut thoracotomy is, to my mind, unforgivable if you can find a method of avoiding that.

Dr. M. Riquet (Paris, France): In our experience, we think that the prognosis of N2 disease is dependent upon the anatomical location of the chain involved, and we have demonstrated that the prognosis does not depend upon the number of nodes involved in these chains, the size of the nodes, and the rupture, or not, of the capsule. So it is indeed the same when two anatomical chains are invaded — and the prognosis is worsened in those cases. I would like to know if you have made this difference between anatomical chains, because mediastinoscopy does not preclude surgery if there is only one chain involved, even if the nodes are big and bulky.

Dr. De Leyn: We found no difference in survival when one nodal station was involved compared with the involvement of multiple nodal stations. In the literature some authors find differences and others don’t.

Dr. D. Branscheid (Grosshansdorf, Germany): Performing a consequent lymph node dissection in N2 stage means finding N3 nodes in a certain number of cases. How often did you find N3 stages? Mediastinoscopy cannot discover all the nodes in all regions, for example, the aortic arch region.

Dr. De Leyn: I know that contralateral mediastinal nodes were involved in a few patients, but I can’t put any figures on it. I often find it difficult, after a radical lymphadenectomy, to decide what is right para-tracheal, precarinal or left para-tracheal.