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Result of induction chemotherapy followed by surgery in patients with stage IIIA N2 NSCLC: importance of pre-treatment mediastinoscopy ☆

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Abstract

Objective: Data from the literature indicate that chemotherapy prior to resection may improve the results. However, only few and conflicting data are reported regarding the correlation between downstaging of mediastinal nodes and outcome. The aim of this study was to look at the correlation between downstaging, survival and pre-treatment staging. **Material and methods**: Between March 1995 and August 1998, 46 consecutive patients with pathology proven N2 disease were treated with three cycles of vindesine-ifosfamide-platinum (VIP). All patients underwent a rigorously performed cervical mediastinoscopy. Patients with at least partial response ($n = 26$) were surgically explored. **Results**: The clinical response rate to chemotherapy was 57% (26 patients). Resection was complete in 23 patients (88.5%). Pneumonectomy was performed in 16 patients. In 11 patients (42.9%) the mediastinal nodes (which were positive at mediastinoscopy) had become negative (downstaging group). The projected 2-year survival of resected patients is 41%. Patients with downstaging of nodes had no better survival compared to patients with no downstaging. Patients with involved subcarinal nodes at mediastinoscopy and patients with involvement of more than one level had a worse survival. **Conclusion**: Surgery in N2-patients responsive to induction chemotherapy resulted in a high complete resectability rate. Findings at pre-treatment mediastinoscopy proved to be the most important prognostic factor.

Keywords: Carcinoma; Non-small cell lung; Combined modality treatment; Induction chemotherapy; Lung surgery; N2-disease

1. Introduction

The involvement of mediastinal lymph nodes (MLN) in patients with potentially resectable non-small cell lung cancer (NSCLC) is a very important prognostic factor. Patients with involved ipsilateral mediastinal or subcarinal lymph nodes (N2 disease) diagnosed preoperatively have a low complete resectability rate and a 5-year survival rate of only 9% [8,11,18,25]. Because of this important impact on prognosis, the new TNM classification has recently been modified [13]. Patients with N2 disease are still classified in stage IIIA while patients with T3N0 or T3N1 disease have been migrated into stage IIB.

In patients with N2 disease, induction chemotherapy followed by resection has been shown to be beneficial in 3 small randomized studies [17,21,22] and several phase II studies. However, review of the literature reveals that the pre-treatment staging was often non-invasive with patients believed to have N2 disease on CT findings only [24]. Enlarged nodes on CT scan are inflammatory in 50% of the cases [5] and these patients can in fact have N0 disease with a much better prognosis. Another striking point is the heterogeneity of the groups. Induction chemotherapy was often administered for stage IIIA tumours on the basis of T3N0 or T3N1 disease. These patients have a far better prognosis than patients with N2 disease, especially if the T3 factor is caused by resectable chest wall invasion.

The aim of this study is to evaluate the results of surgery after induction chemotherapy in a homogenous group of patients with N2 disease, proven by a meticulously performed invasive mediastinal staging. The effect of downstaging, the number and level of involved nodes at mediastinoscopy, and other different prognostic factors on survival are evaluated.

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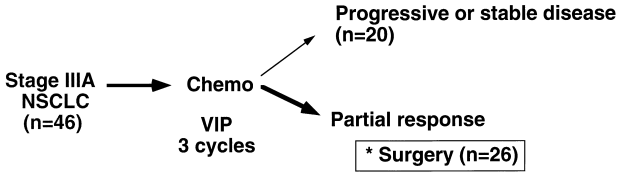

Fig. 1. Flow chart of 46 patients with N2 disease proven by invasive mediastinal staging performed at our hospital.

2. Patients and methods

Between March 1995 and August 1998, patients with potentially operable NSCLC with histological proven N2 disease were entered in this prospective study. Distant metastasis were excluded according to standard guidelines [9]. Since 1998, positron emission tomography (PET) scan was also routinely used in these patients.

As mediastinoscopy is essential to rule out contralateral disease (N3 disease) and because we were interested to evaluate the effect of the number and type of levels involved at mediastinoscopy on survival, we included only these patients who underwent cervical mediastinoscopy in our hospital. During this procedure, the upper right and left paratracheal nodes, the lower right and left paratracheal nodes, and the subcarinal nodes were extensively biopsied and labelled separately [4]. In patients with left upper lobe tumours with clinical suspicion of positive nodes in the paraaortic level or in the aortopulmonary window, a left anterior mediastinotomy was performed in case of negative cervical mediastinoscopy.

Inclusion criteria for induction chemotherapy were: age 70 or less, WHO performance status less than 2, bi-dimensionally measurable disease, no previous radio- or chemotherapy, no previous malignancies. Base line organ functions had to be normal. After combined treatment, patients were followed every 3 months with a thorough clinical examination, biological tests, a chest X-ray, and other imaging studies as clinically indicated or necessary to assess the site of recurrence. The cause of death was determined in all cases.

Tumours were staged according to the revised version of TNM staging, published in August 1997 [15,16].

Table 1
Patient characteristics

	Number	%
Patient number	26	
Median age in years (range)	60.5 (40–75)	
Male	21	80.7
Histology		
Adenocarcinoma	10	38.5
Squamous cell carcinoma	6	23
Large cell carcinoma	10	38.5
Right sided tumour	16	61.5
Left sided tumour	10	38.5
Clinical stage		
cT1N2	4	15.4
cT2N2	15	57.7
cT3N2	7	26.9
Subcarinal level involved at mediastinoscopy		
Yes	11	42.3
No	15	57.7
Number of involved levels at mediastinoscopy		
One	19	73.1
Two	5	19.2
Three or more	2	7.7

2.1. Chemotherapy

Three courses of chemotherapy were given, except in cases with obvious progression during treatment. Cisplatinum 40 mg/m^2 was given on day 1, 30 mg/m^2 on days 2 and 3. Ifosfamide 1200 mg/m^2 was given on days 1, 2 and 3. Vindesine 3 mg/m^2 (max 5 mg) was given weekly during the first cycle and every 2 weeks in cycles 2 and 3. More detailed information on the induction scheme and its morbidity has been published by our respiratory oncology group [26].

Response was assessed at the weekly tumour round by clinicians and a staff member in thoracic radiology, by comparing the bi-dimensionally measurable lesions on a thoracic CT-scan before and 2–4 weeks after the last chemotherapy. The usual criteria for definition of response were followed [14].

2.2. Surgery

Patients with at least partial response underwent surgery with systematic mediastinal lymph node dissection [27].

Resection was defined complete in case of removal of all tumour at the primary site and lymph nodes, with the resection margin negative, and the highest mediastinal lymph nodes free of tumour.

Adjuvant thoracic radiotherapy (a total dose of 56 gy in 28 daily fractions) was given to patients with persistent N2 disease in the resected specimen.

2.3. Statistics

Survival was calculated from the time of diagnosis to the date of death or last date of follow-up for surviving patients. Survival curves were calculated by the Kaplan–Meier product-limit method and compared using the log rank test statistic.

3. Results

3.1. Patients

Between March 1995 and August 1998, 46 patients with histology proven NSCLC with N2 disease were entered in this prospective study. Partial or complete clinical response to chemotherapy was found in 26 patients (57%, Fig. 1).

Table 2
Pathological evaluation of tumour downstaging in patients responsive to chemotherapy ($n = 26$)

	Number	%
N2 → N0 and N1	11	42.3
N2 remained N2 disease	15	57.7
Stage IIIA → stage 0	1	3.8
Stage IIIA → stage I	7	26.9
Stage IIIA → stage II	3	11.5

These 26 patients underwent resection after induction chemotherapy. Patient characteristics are presented in Table 1. Histology was large cell carcinoma in ten patients, adenocarcinoma in another ten patients and squamous cell carcinoma in six patients. At cervical mediastinoscopy, one nodal level was involved in 19 patients, in five patients two levels were involved and in two patients more than two levels were involved. In 11 patients, the subcarinal nodes were involved.

3.2. Surgery

In 16 patients a pneumonectomy needed to be performed, in ten patients the tumour could be cleared by lobectomy. A systematic mediastinal nodal dissection was always done. Complete resectability rate, defined as the number of complete resections over the number of surgical explorations, was 88.5% (23 patients). In three patients the resection was defined incomplete because the highest MLN proved to be positive. In two patients, the tumour and mediastinal nodes were resected, but the highest mediastinal lymphnodes were positive. In one patient, massive extracapsular spread of lymph nodes made complete resection impossible. According to the surgeon, the resection was technically more demanding because of extensive fibrosis in nine patients (34.6%). After pneumonectomy, the bronchial stump was covered with intercostal muscle in 12 patients (75%) and with pericardial fat pad in the four other patients. After lobectomy, the bronchial stump was covered with pericardial fat pad in five patients and with pleura in five patients.

There were no postoperative deaths. The mean hospital stay was 13.6 days ($\pm$ 10.7) except for one patient in which prolonged ventilation was necessary because of pneumonia with respiratory insufficiency (120 days). Other complications were pneumonia and respiratory insufficiency requiring prolonged ($>$ 48 h) ventilation in another two patients, atrial fibrillation in two patients, prolonged air leak in two patients and recurrent nerve palsy in one patient. There were no bronchial fistulae.

3.3. Effect of chemotherapy on downstaging.

The results of the pathological examination of the resected specimens are shown in Table 2. In eleven patients (42.3%), no tumour was found in any of the mediastinal lymph nodes. Complete pathological response (pT0N0) was seen in only one patient (3.8%). In two patients, the tumour in the lung was completely sterilized while the mediastinal nodes remained positive. Pathological T staging was: pT0 in three patients, pTl in 11 patients, pT2 in 9 patients and pT3 in three patients.

3.4. Survival.

The overall 2-year survival in operated patients was 41% with a median survival of 20 months (Fig. 2). In this analysis, the survival in patients with right sided tumours was not different from patients with left sided tumours (2-year survival of 44 and 38%, respectively). Patients with lobectomy

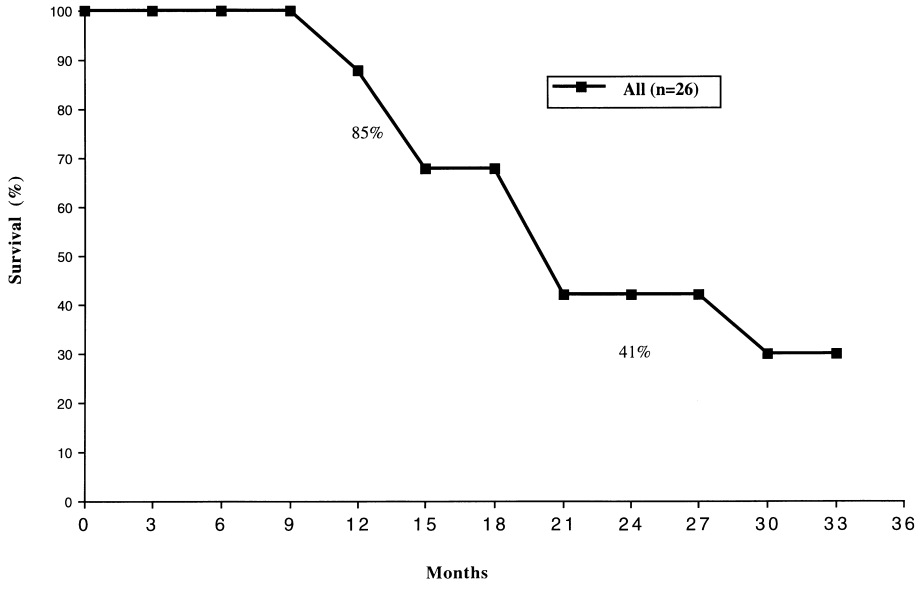

Fig. 2. Overall survival after resection in responding patients treated with induction chemotherapy for N2 disease.

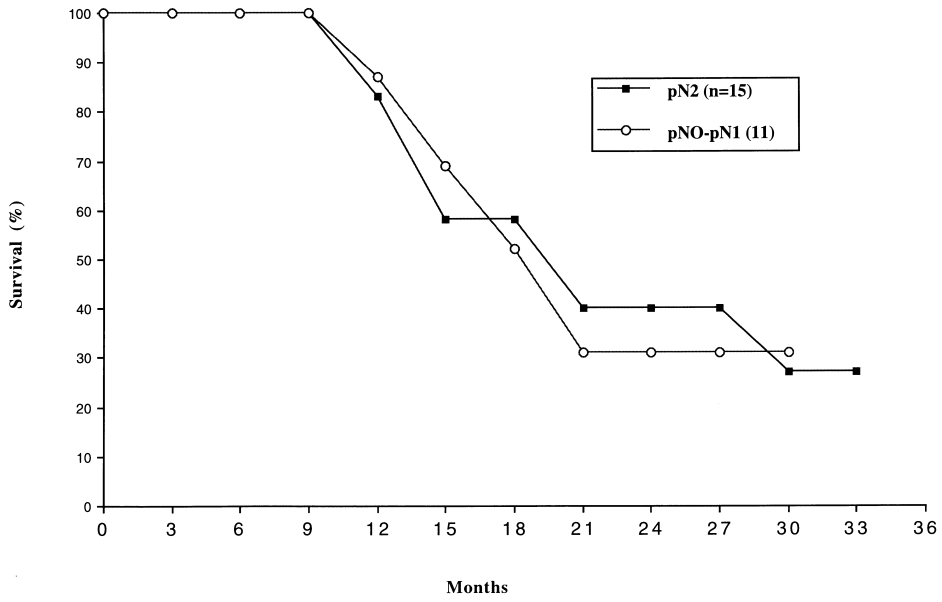

Fig. 3. Survival in patients with persistent N2 disease compared with those patients with downstaging in the mediastinal nodes of the resection specimen in responding patients treated with induction chemotherapy for N2 disease.

tended to have a better survival although the difference was not statistically significant different (2-year survival of 49% and 38% respectively).

Patients with persistent N2 disease had a similar survival than patients with downstaging in these nodes (Fig. 3, 2-year survival of 40 and 31%, respectively). When the subcarinal nodes were involved at the initial mediastinoscopy (before the onset of chemotherapy), survival was significantly lower (Fig. 4) when compared to patients without involved subcarinal nodes. All patients with involved subcarinal nodes were dead by 21 months while the 2-year survival of patients with involvement of other nodal level was 67% ($P < 0.05$).

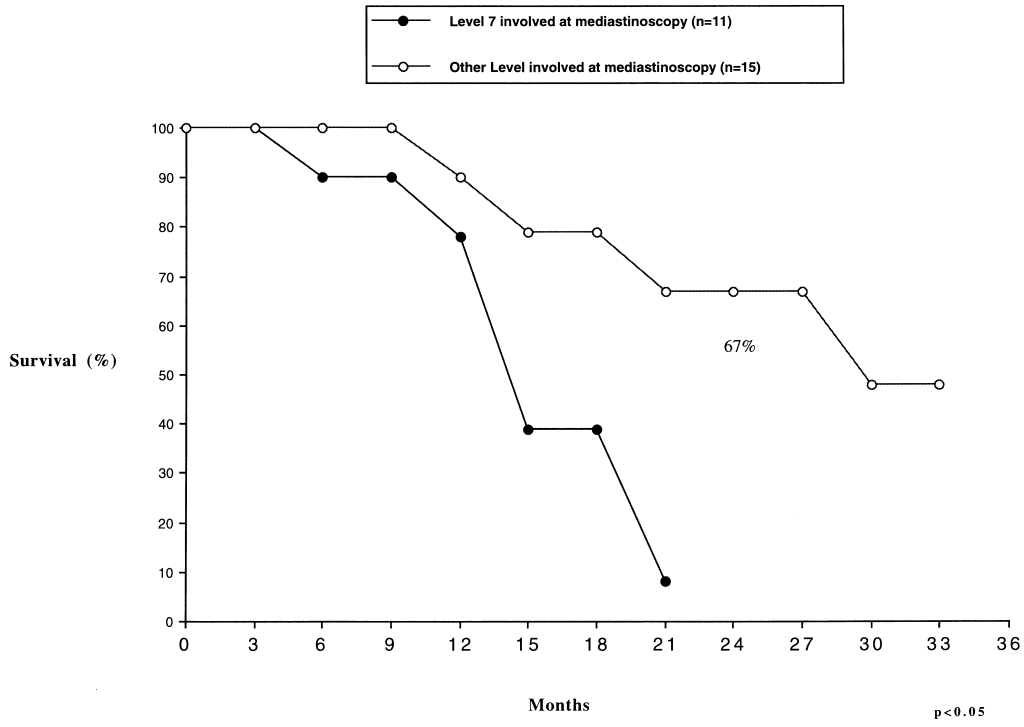

Fig. 4. Survival after resection in responding patients treated with induction chemotherapy for N2 disease. Effect of number of subcarinal lymph nodes at mediastinoscopy.

Patients with only one nodal level involved at mediastinoscopy had a better prognosis when compared to patients with two or more levels involved (2-year survival of 56 and 0%, respectively).

4. Discussion

In this prospective study, we evaluated the results of surgery after induction chemotherapy in patients with NSCLC and N2 disease proven by invasive mediastinal staging. During cervical mediastinoscopy, all mediastinal nodal levels were rigorously biopsied to exclude contralateral disease and to analyse the effect of the sites and number of involved nodal levels on survival after induction chemotherapy. In several phase II studies [18,20,21,23], invasive staging was not performed and N2 disease was based on CT scan findings only! In other studies, findings of cervical mediastinoscopy were not described in detail.

In our study with VIP induction, the response to chemotherapy was 57%, which is comparable to the figure previously described by our group [26]. This clinical response rate is somewhat lower than reported in other studies which use other chemotherapy schemes [12]. Using induction chemoradiotherapy response rates up to 88% [13] and 89% [28] are reported. In a recent study using induction chemoradiotherapy, a pathological complete response of 26% has been reported [6].

We have only explored those patients with at least partial response on chemotherapy ($n = 26$). Some groups have, in an attempt to salvage as many patients as possible explored patients with stable disease. However, when we review the literature [24], pathological complete response is very exceptional in clinically non-responding patients.

Complete resection, which was defined as removal of all known disease with no involvement of the margins of resection, nor of the highest mediastinal lymph nodes was possible in 23 patients (88.5%). The complete resection rate in the literature varies between 65 and 94%. This high resectability in our study is explained by the fact that we explored only patients with radiographic response to the induction treatment. In the study by Elias et al. [7], complete resection was statistically significant higher in patients with radiographic response compared to patients with stable disease.

During thoracotomy, pulmonary resection with systematic nodal dissection was performed. In the majority of those patients (61.5%) a pneumonectomy needed to be performed. When the tumour is located in the upper lobe, a lobectomy with mediastinal lymphadenectomy is performed. We believe that covering of the bronchial stump after pneumonectomy (mainly on right side) is essential to prevent bronchial fistulae.

The 2-year survival in our study was 41% with a median survival of 20 months. We have to keep in mind that this survival rate is obtained only for the subselected group of 26 responding patients. Although mediastinal nodal dissection is easier and more extensive to perform on the right side, no difference in survival was found between left or right sided tumours. Patients in which the tumour was cleared by lobectomy had a better survival when compared to patients with pneumonectomy. In three of these patients, pre-treatment staging showed that pneumonectomy would be necessary, but after induction treatment the tumour could be resected by lobectomy. All three patients are alive without evidence of disease.

Pathologic complete response (PCR), as defined by no viable tumour in resected specimen (primary tumour and dissected nodes) is an important endpoint associated with event free survival. In reported series, the incidence of PCR ranges from 0 to 18%. In the retrospective study of Memorial Sloan Kettering Cancer Center [19], patients with PCR had a progression-free survival of 45% at 5 years. In our series, only one patient (3.8%) had no viable tumour after three cycles of VIP.

Downstaging (mediastinal nodes negative in patients when previously involved) could be an important prognostic factor for resectability and long-term survival although many trials are unevaluable for this analysis as detailed mediastinal staging is not routinely performed and reported. In our study, downstaging in patients responsive to chemotherapy ($n = 26$) occurred in 11 patients (42.3%). This is lower when compared to the study of Elias (71%) in which cisplatinum, Leukovorin and 5-FU was given [7] but comparable with the study of Kim et al. [10]. In this study, downstaging was described in 41%. To our surprise, patients with downstaging had no better survival compared to patients in which the mediastinal nodes remained positive. In the study of Elias et al., patients with downstaging showed a trend (but not statistically significant) to better survival. Chella [3] reported no difference in survival in pN2 and pN0 patients. In the Southwest Oncology group trial 88-05 [1], 126 patients with stage IIIA (N2) or stage IIIB (N3 or T4) were treated with preoperative chemoradiotherapy. The strongest predictor of event-free survival in this study was the absence of involved mediastinal nodes at the time of surgery.

In our study, the effect of pathological downstaging was not a significant prognostic factor on long-term survival. We have no clear explanation for this finding. A possible explanation could be that only patients with response to chemotherapy were explored in our series. Another possible explanation is the use of high-dose postoperative radiotherapy in patients with remaining viable tumour in the mediastinal nodes of the resection specimen. This has, however, been done in most of the studies. Conformation of this finding might have considerable implications for the future. According to our preliminary results, patients with persistent mediastinal disease might have a similar survival.

In two patients, the tumour in the lung was completely sterilized while the mediastinal nodes remained positive, which stresses the need that mediastinal nodal dissection should be performed in all patients.

In all patients in this series, meticulous cervical mediastinoscopy was performed at our hospital. This allows analysis of the correlation between downstaging and mediastinoscopic findings on survival. A very important prognostic factor for survival was the result of cervical mediastinoscopy performed before the onset of induction chemotherapy. Patients in which the subcarinal nodes were positive at mediastinoscopy, had a significantly lower survival with no patients alive at 2 years. Patients with more than one nodal level involved at mediastinoscopy, also had a significantly lower survival when compared to patients with only one nodal level involved.

We conclude that surgery after induction chemotherapy can be performed with acceptable morbidity. To our surprise, downstaging of the mediastinal nodes was not a prognostic factor in this analysis while the findings of cervical mediastinoscopy before the onset of induction chemotherapy proved to be of critical importance. Larger studies are needed to evaluate the impact of staging procedures and surgical resection of surgery in this group of patients.

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Appendix A. . Conference discussion

Dr T. Grodzki (*Szczecin, Poland*): I have one doubt about those disappearing carcinomas in N2 disease, because the number of 32% N2 lymph nodes which were finally concluded with absence of malignant cells is a little bit too high. Did you do the histologic findings with the cytokeratin reaction or another specific monoclonal antibody's reaction, because the result seems a little bit false.
Dr De Leyn: Excuse me, I did not understand the question.
Dr. Grodzki: I wonder why 45% of first N2 disease at the end has appeared to be N1 or N0 disease?
Dr. De Leyn: All patients had N2 disease proven by cervical mediastinoscopy before the onset of chemotherapy. Then they received chemotherapy. After chemotherapy downstaging may occur. This means that these nodes, which were positive, become negative because of the chemotherapy. In the literature this varies from 40 to 70%.
Dr. Grodzki: Yes, but you have indicated that downstaging has no influence on 5-year survival, so it seems to confirm the thesis that the downstaging was a little bit false. So my question is, what techniques of histologic examination were used to prove the absence of malignant cells?
Dr. De Leyn: Well, we did not do immunohistology, we just did routine histology.
Dr. P. Van Schil (*Edegem, Belgium*): I have a rather similar question and one comment. In contrast to previous studies, you did not find a better survival when there was a downstaging to N0 or N1 disease. Do you have an explanation for that? My comment is that a definite answer, whether surgery or radiotherapy is better after response to induction chemotherapy, can only come from large phase 3 studies. There is currently a study from the EORTC trying to answer that. In this study, patients who have a response to induction chemotherapy with proven N2 disease beforehand, are randomized between surgical treatment and radiotherapy. I would encourage the audience to participate in that study because we need quite a lot of patients, as this is a prospective randomized study.
Dr. De Leyn: I fully agree that it is very remarkable that we found no effect. When you look through the literature, there is an article published by Chella, which also found no difference. In previous studies, not all patients had cervical mediastinoscopy, and there are only a few groups which are looking at the effect of downstaging of mediastinal nodes. I fully agree that it is difficult to understand and we have to do more extensive studies to see if indeed surgery is necessary.
Dr A. End (*Vienna, Austria*): Could you comment on your postoperative adjuvant therapy?
Dr De Leyn: When we found persistent N2 disease, these patients received radiotherapy up to 56 gray. This could be an explanation as to why we did not find an effect of downstaging on survival.
Dr A. Brutel de la Riviere (*Nieuwegein, The Netherlands*): When do you determine the operative strategy? I mean, do you determine the resection planned before the chemotherapy is started or after you have noted response and, therefore, surgery is, in your view, possible?
Dr De Leyn: In our center, all patients are shown on a multidisciplinary group, and induction chemotherapy is given when we think, as surgeons, that the tumour is resectable. If you ask, are you going to do a lobectomy when initially findings had shown that the tumour could only be cleared by a pneumonectomy, that is a difficult question. Initially, we always did what we should have done before, chemotherapy. During the last months, if the tumour has decreased that much, we will try to do a less extended resection, if it is possible. We found a good survival in these patients with lobectomy. So it seems that you can do a less extended resection.