Results of induction chemotherapy followed by surgical resection in patients with stage IIIA (N2) non-small cell lung cancer: the importance of the nodal down-staging after chemotherapy

Luca Voltolini*, Luca Luzzi, Claudia Ghiribelli, Piero Paladini, Maurizio Di Bisceglie, Giuseppe Gotti

Thoracic Surgery Unit, University Hospital of Siena, Viale Bracci n. 1, 53100 Siena, Italy

Received 10 October 2000; received in revised form 9 May 2001; accepted 16 July 2001

Abstract

Objective: Chemotherapy of stage IIIA non-small cell lung cancer (NSCLC) using second generation, cisplatin-based combinations has shown to improve the results; however, the distant relapses remain the major problem. Encouraging results in the treatment of stage IV NSCLC with newer agents (gemcitabine, paclitaxel) has encouraged us to use them in stage III. The aim of this study was to assess feasibility and efficacy of induction chemotherapy with cisplatin and gemcitabine followed by surgery for patients with stage IIIA (N2) NSCLC.

Methods: From February 1996 to December 1999, 36 consecutive patients with mediastinoscopically staged N2 NSCLC received three cycles of cisplatin (80 mg/m², day 2) and gemcitabine (1200 mg/m², day 1 + 8) followed by surgery in responding patients. Patients with stable disease or even local progression received radiotherapy. All patients had clinical N2 disease (mediastinal lymph nodes metastasis) observed on CT scan.

Results: No major complications of the chemotherapy occurred. Twenty-five patients (70%) had a clinical partial response and were surgically explored, with 18 complete resections (70%). There were no in-hospital deaths, although four (16%) major complications: bronchopleural fistula (two), respiratory insufficiency (one), oesophagopleural fistula (one). In the total group of 36 patients, 3-year survival was 20%. So far, no patient without surgery has survived longer than 27 months; median survival was 8 months. In the group of the 25 patients who underwent surgery 3-year survival was 30%, with a median survival of 21 months. The difference is significant ($P = 0.0027$). In the surgical group, the survival of patients with down staged disease (56%) was greater than that of patients with persistent N2 disease (44%) after chemotherapy (3-year survival of 59 and 0%, respectively; $P = 0.0013$). Conclusion: induction chemotherapy with cisplatin and gemcitabine resulted in major tumour regression in a large percentage of patients with clinical N2 disease. In responding patients both the complete respectability rate and survival were higher when compared to historical controls. Survival was significantly better in patients down-staged to a mediastinal negative disease.

Keywords: Non-small cell lung cancer; Induction chemotherapy; N2 disease; Combined modality treatment

1. Introduction

Single modality therapy in stage III A (N2) non-small cell lung cancer (NSCLC) is associated with poor survival, with only a minority of highly selected patients achieving a 5-year survival [1,2].

The observation that the failure pattern of N2 disease is mostly distant metastasis has led to the evaluation of a multimodality approach [3–9]. Multiple drug combinations, with varying doses, schedules and number of preoperative and postoperative cycles, different combinations of radio- and chemotherapy have been evaluated. However an optimal treatment approach to stage III NSCLC has yet to be identified.

In the last few years, several promising new drugs with different action’s mechanism and encouraging toxicity profiles such as paclitaxel, vinorelbine and gemcitabine have demonstrated significant activity in advanced inoperable NSCLC. We then decided to use as induction treatment the cisplatin gemcitabine combination because of their synergism or additive effect showed both in vitro and in vivo, with modest toxicity [10].

The most recent studies about neoadjuvant chemo or radio-therapy correctly require the histologically confirmation of N2 disease because the CT scan represents a rough tool to stage the mediastinum. However N2 NSCLC is...
known to be composed of several subgroups with different prognosis. The most favourable outcome occur among patients with minimal N2 disease, (only one positive lower mediastinal node station excluding subcarinal adenopathy and extracapsular spread), whereas bulky/ multilevel N2 disease carries a significant worse prognosis.

Thus, clinical trials dealing with N2 disease should describe the most important clinical prognostic factor (e.g. clinical N2 status, multiple levels of diseased nodes, etc.).

The purpose of this study was to assess toxicity, tumour response, disease control and survival in a homogeneous group of patients with clinical N2 disease (cN2), pathologically confirmed by mediastinoscopy, treated by induction chemotherapy with cisplatin and gemcitabine followed by surgery. The effect of down-staging and other potential predictors of survival were evaluated.

2. Material and methods

2.1. Eligibility

Only patients with mediastinoscopy- proven affected ipsilateral mediastinal lymph nodes were eligible (T1–3, N2). All patients had histologically or cytologically documented NSCLC and cN2 disease based on CT scan. During mediastinoscopy nodes of bilateral stations 2 and 4 and subcarinal station 7, as defined by the American Thoracic Society [11] were biopsied and labelled separately. An anterior mediastinotomy was done for biopsies of station 5 or 6 for left upper lobe lesions, in case of negative cervical mediastinoscopy. Patients with extracapsular and intracapsular lymph node involvement were eligible.

The staging evaluation included history and physical examination, complete blood cell count, serum chemistry tests and urine analyses. To rule out distant metastasis all patients underwent the following investigations: chest X-ray, bronchoscopy, CT scan of brain, chest and abdomen, bone scan and abdominal ultrasound. Tumours were staged according to the revised version of TNM staging published in August 1997 [12,13]. All patients were judged to have adequate lung function for planned surgical resection, with predicted postoperative forced expiratory volume in 1 s (FEV1) greater than 800 ml.

Eligibility criteria also included the following: (1) Eastern Cooperative Oncology Group performance status of 0–1; (2) age between 18 and 75 years; (3) no previous radio- or chemotherapy, no previous malignancies; (4) no other serious medical or psychiatric illnesses.

Required laboratory data included the following: granulocyte count greater than 2000/ml; platelet count greater than 100 000/ml; haemoglobin level greater than 10 g/dl; BUN less than 1.5 times normal; creatinine concentration less than 1.5 mg/dl or creatinine clearance of 60 ml/min and bilirubin level less than 1.5 mg/dl.

Before starting induction chemotherapy all patients were carefully examined by a medical panel composed of a pulmonologist, thoracic surgeon, medical oncologist and radiotherapist to confirm the stage of disease.

Written informed consent was required and obtained from all patients before commencement of therapy.

2.2. Treatment

The treatment protocol is graphically summarized in Fig. 1.

The treatment plan consisted of three preoperative chemotherapy cycles followed by surgery in responding patients within 3–5 weeks after the last chemotherapy. Induction chemotherapy consisted of intravenously cisplatin, 80 mg/m² on day 2, and gemcitabine 1200 mg/m² on days 1 and 8 (cycle repeated every 21 days).

Two to four weeks after completion of the induction chemotherapy all patients were carefully restaged with a CT scan of the chest and upper abdomen, bone scan and CT or MRI of the head. They were also re-evaluated with a second set of pulmonary function studies. Conventional response definitions were used for this CT scan-based clinical response assessment [14]. Patients with at least partial response underwent thoracotomy and attempted standard curative resection with unilateral mediastinal lymphadenectomy. This means all technically accessible hilar and mediastinal nodes were to be resected and labelled according to the American Thoracic Society classification: for right-sided lesions, these were stations 2R, 4R, 7, 8, 9 and 10R; for left-sided lesions, 2L, 4L, 5, 6, 7, 8, 9 and 10L [11].

Postoperative mediastinal radiotherapy, starting 4 weeks after surgery, with a total dose of 59.4 Gy at 18 Gy per fraction once a day, was recommended to patients with viable tumour in N2 nodes at pathologic examination of
resected material or incomplete resection. Target volume included the bronchial stump, ipsilateral hilum, involved mediastinum and the sites of gross residual tumour.

In cases of stable disease or even local progression, the same dose of radiotherapy was administered.

After completion of treatment patients were followed up at 3 months interval for the first 2 years and twice yearly thereafter. Investigations included physical examination, complete blood cell count, serum chemistry and chest radiograph. Bronchoscopy and CT scan were only performed if clinically indicated.

Survival was calculated from the first day of chemotherapy until death or the time of evaluation for this report. Survival curves were constructed using the Kaplan–Meier method [15] and compared using a long-rank test [16]. Results were analyzed as of February 28, 2000.

3. Results

3.1. Patients

From January 1996 to December 1999, 36 patients with cN2, histologically confirmed, NSCLC, examined at the Thoracic Surgery Unit, University Hospital of Siena, were entered into this prospective study. There were 30 men (83%) and 6 women (17%) with a median age of 63 years (range 45–74 years). All patients studied were Eastern Cooperative Oncology Group performance status 0–1.

The histologic diagnosis was squamous cell carcinoma in 18 patients (50%), adenocarcinoma in 15 (42%) and large cell carcinoma in three (8%). The primary tumour was located in the right lung in 26 patients and in the left lung in ten. At the start of chemotherapy, the primary tumour was classified clinically as T1 in two patients (6%), T2 in 20 (55%) and T3 in 14 patients (39%).

All patients presented evidence of multiple enlarged mediastinal lymph nodes on CT scan of the chest. N2 disease was histologically confirmed in all patients by mediastinoscopy or anterior mediastinotomy, that revealed that only one level of N2 nodes was affected in 11 patients, two levels in 20 and more than two levels in five. The subcarinal nodes were involved in 17 patients.

3.2. Induction chemotherapy

All 36 patients completed the three planned chemotherapy cycles. There were no deaths directly related to induction chemotherapy. One patient died at home after completion of induction chemotherapy, from a pulmonary embolus. This was not considered a treatment related death. No patient was removed from the study due to any toxic effects of chemotherapy. The most common toxicity was myelosuppression. Grade 3 and grade 4 neutropenia was seen in 23% and 3% and thrombocytopenia grade 3 and 4 in 25% and 14% of cases, respectively. Non-haematologic toxicity consisted of nausea and vomiting (18%, grade 1–3), renal toxicity (35%, 1–2) and neurotoxicity (38%, 1–4).

3.3. Clinical response

None of the patients had radiographic complete response to preoperative chemotherapy. Twenty-five patients (70%) achieved a partial response. Among the 11 patients who did not demonstrate a clinical response, nine (25%) had stable disease and two (5.5%) had disease progression (one increase in size of the primary tumour and one distant metastasis). On the bases of this restaging the 25 patients (70%) with clinical partial response were judged suitable for surgical treatment.

The characteristics of these patients are listed in Table 1. Importantly, based on findings at mediastinoscopy, only three patients could be classified in the most favourable subset of patients with N2 disease (minimal N2 disease).

3.4. Surgery

Surgical procedure included standard lobectomy (n = 8), lobectomy and chest wall resection (n = 1), lobectomy and sleeve resection of the pulmonary artery (n = 1), bilobectomy (n = 2), simple pneumonectomy (n = 8), intrapericardial pneumonectomy (n = 3). Two patients had a thoracotomy exploratory only. The bronchial stump was covered with a viable pedicle of tissue in all but four patients. The pericardium was used in nine patients, the parietal pleura in seven and the azigos vein in three. A unilateral mediastinal nodal dissection was done in all 23 cases of pulmonary resection.

In 18 patients the resection was more difficult than usual, because of the mediastinal fibrosis as a response to the therapy and consequent obliteration of tissue planes.

Seventy-two (18/25) percent of patients undergoing surgical exploration had complete resection, i.e. 50% of the whole cohort (18/36). Seven patients had an incomplete resection: three patients had a diseased microscopic margin; two, a diseased highest node resected; and two patients had

| Table 1 |
| Characteristics of resected patients (n = 25) |
| Median age in years | 64 | Range 47–73 (%) |
| Male | 21 | 84 |
| Histology |
| Adenocarcinoma | 11 | 44 |
| Squamous cell carcinoma | 12 | 48 |
| Large cell carcinoma | 2 | 8 |
| Clinical stage |
| cT1N2 | 2 | 8 |
| cT2N2 | 13 | 52 |
| cT3N2 | 10 | 40 |
| Number of involved nodal levels at mediastinoscopy |
| One | 9 | 36 |
| Two | 12 | 48 |
| Three or more | 4 | 16 |
exploratory thoracotomy only because of massive extra capsular spread of lymph nodes. No deaths occurred in the postoperative period. Mayor postoperative complications occurred in four patients (16%): bronchopleural fistula and empyema \((n = 2)\), oesophago-pleural fistula \((n = 1)\) and respiratory failure \((n = 1)\). Minor complications included prolonged air leak in one patient and atelectasis requiring bronchoscopy in one.

### 3.5. Pathologic response

The degree of tumour down staging was assessed by a meticulous evaluation of the primary lesion, hilar lymph nodes and labelled mediastinal lymph nodes. The number of mediastinal lymph nodes examined was an average of 16 (range 12–34). Complete pathologic response \((pT0N0)\) was found in two patients \((8\%)\). Ten additional patients had no evidence of tumour in any examined lymph node but did have evidence of residual tumour in the primary site. Two patients had residual tumour in the primary site with only N1 nodes having evidence of tumour. Overall, 14 patients \((56\%)\) had sterilization of previously affected mediastinal lymph nodes. Clearance of metastatic disease from the regional lymph nodes was the mayor factor for tumour down staging, that was as follows: from stage IIIA \((N2)\) to stage II \((N1)\) in 8% \((2/25)\); from stage IIIA to stage I \((N0)\) in 40% \((10/25)\) and from stage IIIA to stage 0 \((T0N0)\) in 8% \((2/25)\). Eleven \((44\%)\) of all patients who underwent surgery showed no change in the stage of disease.

The planned postoperative radiotherapy dose of 59.4 Gy was administered to seven out of 11 patients who had had an incomplete resection or persistent N2 disease. Radiotherapy was not given to four patients for the following reasons: slow recovery from surgery \((n = 3)\), disease progression with distant metastasis \((n = 1)\). Among those patients who did not undergo surgery, seven patients with stable disease and the patient with local progressive disease received complete radiation dose.

### 3.6. Survival

In the total group of 36 patients, 3-year survival was 20% with a median survival of 18 months (Fig. 2). Mean follow-up of the surviving patients was 22 months, and that in the whole group was 16 months. So far, no patient without surgery have survived longer 27 months, only one patient is still alive after 16 months from the first day of chemotherapy. Median survival was 8 months. In the group of the 25 patients who underwent surgery 3-year survival was 30% with a median survival of 21 months. The difference is significant with \(P = 0.0027\) (Fig. 3). Of these 25 patients, at the median follow up of 19 months, 12 patients \((48\%)\) were alive, three with recurrent or persistent disease. Of 13 \((52\%)\) deaths, ten were from recurrent disease and three were unrelated. Sites of initial failure included only loco regional in one patient, only systemic (excluding brain) in four, only brain in five and both local and systemic in three.

In the surgical group, the survival of patients with down staged disease was greater than that of those patients with persistent N2 disease \((3-year survival of 59 and 0\%, respectively; P = 0.0013)\) (Fig. 4).

Analysis of the survival for patients with involvement of only one level of mediastinal lymph nodes at cervical mediastinoscopy compared to those with involvement of two or more levels, showed no statistical difference between the two groups. However a trend towards improved survival was evident in patients with involvement of only one level of mediastinal lymph nodes (Fig. 5). Patients with involve-
ment of subcarinal lymph nodes at cervical mediastinoscopy had significantly lower survival when compared to patients without involved subcarinal nodes (3-year survival of 14 and 49%, respectively; \( P = 0.036 \)) (Fig. 6). There was no difference in survival between patients with squamous cell carcinoma and those with adenocarcinoma. There was also no difference by histology in frequency of down staging or resectability rate.

4. Discussion

Single modality therapy with either surgery or radiation is curative for a very small fraction of patients, who present stage IIIA (N2) NSCLC. Surgery is able to cure patients who have a negative mediastinoscopy and are found on surgical exploration to have a single microscopically involved node station [2]. Radiation therapy cures only less than 10% of patients [17].

Results of neoadjuvant therapy are encouraging in that chemotherapy response rates are considerably higher in this patient population than in patients with metastatic disease with some pathologic complete responses; moreover long-term survivors have been reported in nearly every combined modality therapy trials. Are these long-term survivors patients with minimal N2 disease or are they patients with multilevel or bulky mediastinal disease? Stage IIIA patients with minimal N2 disease have a 5-year survival rate of 15–30% after surgery alone, results not different from that of combined modality therapy [18–20]. This, therefore, emphasized the need to carefully define what subset of stage IIIA (N2) disease has been studied. In this prospective study, trying to keep the patient population as homogeneous as possible, only patients with clinical N2 disease (based on CT scan) and histologically proven by invasive mediastinal staging, were entered. During cervical mediastinoscopy we always performed a mediastinal lymph node mapping to analyze the sites and number of involved nodal levels on survival after induction chemotherapy. Among patients who underwent surgery a single node was found to be affected at preoperative cervical mediastinoscopy in nine patients. Among these, only three patients could be classified in the most favourable subset of patients with N2 disease (minimal N2 disease). The other 16 patients had two or more nodal levels involved. Nine patients had involvement of subcarinal lymph nodes. Although the number of patients is too low to draw definitive conclusions, these results of cervical mediastinoscopy seem to be an important prognostic factor for survival. In fact, patients with involved, subcarinal nodes had a significant lower survival and patients while only one nodal station involved, compared to patients with two or more nodal levels involved showed a trend towards improved survival.

At present, there are many unresolved questions regarding the optimal induction strategy. The introduction of new less toxic and more active agents has led us to use only chemotherapy as induction therapy, even if the best phase II results are those obtained with combined chemo radiotherapy. Radiotherapy undoubtedly increases toxicity, while chemotherapy alone potentially allows a greater dose usage; this is worthwhile since the vast majority of stage IIIA (N2) patients die of systemic recurrent disease. Our results demonstrate that cisplatin gemcitabine combination as induction chemotherapy is well tolerated and quite active. Only a minority of patients developed a symptomatic grade 4 neutropenia and/or thrombocytopenia. No deaths related to the treatment occurred and neither did any occur in the postoperative period. The overall morbidity was quite acceptable. Two patients developed a small bronchopleural fistula that healed in both cases with chest drainage alone. One patient had undergone a right pneumonectomy and had the bronchial stump covered with pleura. The other patient had undergone a right upper lobectomy and no coverage of the bronchial stump was used. Another patient developed a late oesophagopleural fistula after she went home. She came back after 10 days from discharge with a high fever. We think that the extended lymphadenectomy had provoked the fistula. Seventy percent of patients showed a clinical response, that is comparable to the figure previously reported in literature, although some authors report response rates up to 88% [4] using induction chemo radiotherapy.

We considered it rational to operate on only those patients with at least partial response since as eligibility criteria, our patients presented cN2 disease, with the major part of the

---

**Fig. 5.** Survival after resection in responding patients (\( n = 25 \)) with involvement of only one nodal level verses more than one level at cervical mediastinoscopy.

**Fig. 6.** Survival after resection in responding patients (\( n = 25 \)) with or without involvement of nodal level 7 at cervical mediastinoscopy.
them having bulky/multilevel N2 disease and then an inoperable disease. Because there is no obvious correlation between radiologic and histologic response, many Authors submit to surgery also those patients with stable disease. However, long-term survival can only be obtained after complete resection. In this study, the complete resection of 70% in patients with cN2 disease is high, considering that, in the series, without neoadjuvant chemotherapy, it varies from 18 [1] to 65% [2].

Pathologic complete response (PCR) is an important endpoint associated with long-term survival, as reported by several groups [3,5,6] and emphasized by Pisters et al. [21] that reported a 5-year survival rate of 54% in patients with PCR. In our study only two patients (8%) had no viable tumour in the resected specimens after three cycles of chemotherapy. This is somewhat lower than earlier reports [3,6]. Of major importance, however, was the number of patients in our study whose disease was down staged on the basis of negative mediastinal nodes (56%).

We found nodal down staging at the time of surgery to be the strongest predictor of prolonged survival. In fact, patients with pathologically negative mediastinal nodes at the time of surgical resection had four times the median survival of those with residual involved nodes (3-year survival, 59 versus 0%, \( P = 0.0013 \)). Using only chemotherapy as induction treatment, this data could suggest that clearance of tumour in the mediastinal lymph nodes may serve as a positive sign of the possibly eradication of micro-metastasis. The patients not down staged do not greatly benefit from surgical resection. Restaging was performed in our study by CT scan, as in the mayor part of the trials. However, CT scan remains an inexact method of restaging these patients and often underestimates the degree of local tumour regression [6]. Thus, effort should be made to improve the accuracy of restaging before proceeding to resection. Preliminary pilot studies suggest that positron emission tomography (PET) scanning will be superior to the conventional CT scan in assessing the mediastinum. It may be particularly helpful after induction chemotherapy to determine if residual CT abnormalities in the mediastinum repreme a viable tumour. VATS, also, could be useful in restaging these patients.

The distant recurrence rate of 48% is disappointing. Whether additional cycles of preoperative and postoperative chemotherapy might reduce the incidence of distant disease remains speculative. Frequent isolated brain metastases (five cases in our series) raises the question on whether prophylactic cranial irradiation should be incorporated into further studies.

The most important data to judge a study about neoadjuvant chemotherapy is long-term survival. Our study is to small with only intermediate follow up to allow us to draw definitive conclusions; moreover the observed 3-year survival of 30% has been obtained only for a sub-selected group of 25 responding patients, with a good performance status. However, this survival rate seems to represent a significant improvement when one considers that surgery or radiotherapy alone survival of less than 15% at 2 years can be expected in patients with both cN2 status and pathological multiple N2 nodes [1].

In conclusion, induction chemotherapy with cisplatin and gemcitabine resulted in major tumour regression in a large percentage of patients with cN2 NSCLC, without significant toxicity. In responding patients both the complete resectability and survival were higher when compared to historical controls. Survival was significantly better in patients down-staged to a mediastinal negative disease. Distant recurrence remains a significant problem. Further investigations should address if more cycles or a higher dose of chemotherapy would be useful.

References

I don’t have a big experience with this procedure. I’m not too sure that it would be so useful, even though I know that some surgeons have performed a mediastinoscopy with good results. I think, because of scar and fibrosis that you will find in the mediastinum, it’s difficult to correctly assess the importance of the disease, the involvement of mediastinal lymph nodes.

Dr T. Dosios (Padova, Italy): My question is a little bit similar to Dr Rea. You trusted the radiological response, but what about the cytological response, the pathologic response? I think that we need to know if these lymph nodes are positive or not after induction therapy. The only way to obtain this information is to have a redo mediastinoscopy. But I realize that redo mediastinoscopy is difficult, so my suggestion is to avoid mediastinoscopy during the pre-induction evaluation of the patient. If we have a patient with a CT scan showing enlarged lymph nodes, we should try to obtain histology of these lymph nodes by using less invasive methods; for example, transbronchial needle biopsy or transesophageal needle biopsy. In that way we can perform a mediastinoscopy after induction therapy much more easily and safely. I think this mediastinoscopy should be done immediately before the operation, at the same session, in order to avoid the additions which make the operation difficult. I have found that it is very difficult to perform a second mediastinoscopy on a patient who was submitted to a first mediastinoscopy 3 months previously and then he was given induction therapy. So my suggestion is to avoid the first mediastinoscopy and to preserve the mediastinoscopy for the post-induction evaluation, immediately before the operation.

Dr Voltolini: I think mediastinoscopy before induction chemotherapy is useful not only to confirm the N2 status, but also to exclude contralateral disease. So if we want to compare a homogeneous group of patients, we must really know what the stage is. We must accurately stage the patient. With transbronchial or transcarinal biopsy you know that patient has N2 disease, but maybe he or she could have N3 disease and we don’t know. So I don’t concur.

Dr A. Poncelet (Brussels, Belgium): I just wanted to know if you did your survival analysis on the 25 patients who were operated on and who had partial or complete response, and, if so, wouldn’t it be more accurate to remove from the analysis the seven patients who had incomplete resection during surgery?

Dr Voltolini: The incomplete resection depends sometimes on the positive or highest mediastinal lymph nodes. So sometimes you perform a radical lymphadenectomy and you will find N2 disease at a high mediastinal level, so L2 or R2 right involvement. In that case you have not achieved a complete resection, but I think it’s a different situation from patients who didn’t respond to induction chemotherapy, So I think we must include these patients in the analysis.

Dr P. Macchiarini (Hannover, Germany): I’m really sorry, but if you are presenting a paper, you don’t need to tell us your impression. You need to tell us the data that you have. The aim of the study was to check on the feasibility to do this induction chemotherapy and surgery for N2 patients. If you include N2 patients who have 1, 2, 3, or whatever level of N2 disease, then you need to operate them because the aim of the study was to do both therapies and not only to operate on partial or complete responder patients because we need to know what happens with the stable disease. Therefore, I would like to suggest that you come back with this information. Either you design a really well-structured protocol to do this study or you please include only partial or complete responders.

I have a comment about no mediastinoscopy at all. I think it is a big mistake. Over two decades we have learned so much about mediastinoscopy. For instance, you cannot anatomically stage a mediastinum through a transthoracic biopsy. And if you want to do this huge operation that the gentleman is presenting, then you need to know if the lymph nodes have involved one or two stations, if this involvement is extracapsular, if tracheobronchial or vascular structures are involved. Moreover, doing a mediastinoscopy is very easy and you need that to exactly prove the results of a phase 2 or a phase 3 trial.