Preoperative Chemoradiotherapy and Surgery for Selected Non-Small Cell Lung Cancer IIIB Subgroups: Long-Term Results

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Background. **Preoperative chemoradiotherapy is feasible for selected patients with non-small cell lung cancer stage IIIb. The aim of this investigation was to analyze long-term results after this multimodality approach and to identify subgroups with improved long-term prognosis.**

Methods. **From March 1991 to June 1996, 56 patients were entered. Three cycles of cisplatin (P) (60 mg/m^2, days 1 + 7) and etoposide (E) (150 mg/m^2, days 3 to 5 qd 22) were followed by one cycle of radiotherapy/chemotherapy (RTx/CTx) (45 Gy, 1.5 Gy bid/3 weeks with P 50 mg/m^2 days 2 + 9/E 100 mg/m^2 days 4 to 6) followed by repeat mediastinoscopy and surgery.**

Results. **There were 46 men and 10 women (age 34 to 69 years, median 55 years; World Health Organization status 0 to 2, median 1). Twenty-eight had T4, and 32 had proven N3, in detail: T4N0/1, 10; T4N2, 14; T3N3, 9; T4N3, 4; and T1/2N3, 19. Thirty-four (61%) were operated on; 27 (48%) were completely (R0) resected. Survival at 5 years is 26% for all, and 43% for R0 patients. Toxicity included two deaths (one septicemia, one anastomosis insufficiency).**

Conclusions. **This intensive program proved to be highly effective in unfavorable IIIB subgroups with promising long-term survival for T4 tumors as well as N3 disease.**

For a long time, standard treatment for stage IIIb non-small cell lung cancer has been radiotherapy alone; but recently, bimodality protocols of chemotherapy combined with radiation have been shown to give improved long-term results [1, 2]. However, after this approach, local control at the primary tumor site still remains insufficient [3]. This has led different investigators to include surgery as definitive local treatment after such a bimodality induction [4–8]. It is still not clear whether this aggressive trimodality approach is prognostically justified in most of these patients. Therefore, results from prospective randomized trials are eagerly awaited. Stage IIIb constitutes of a heterogeneous patient group with tumors of different biological aggressiveness and prognosis (eg, T4N0/1 vs T1N3) [9]. It is also widely accepted that some subgroups of T4 disease can be potential candidates for surgical approaches (T4 carina, T4 satellite nodes), while others are generally not considered for any inclusion of surgery (T4 malignant pleural effusion) [9, 10]. To identify stage IIIb subgroups with improved long-term prognosis, we have analyzed the mature follow-up data from patients prospectively entered onto a trimodality trial with induction chemoradiotherapy followed by definitive surgery.

Presented at the Thirty-fifth Annual Meeting of The Society of Thoracic Surgeons, San Antonio, TX, Jan 25–27, 1999.

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Material and Methods

This prospective single-institution phase II trial was carried out in selected patients with inoperable stage IIIa or IIIb non-small cell lung cancer, and interim results have already been reported [11]. The intention of this investigation was to analyze our more extended subset of IIIb patients up to the inclusion date of June 1996 and consecutive long-term results with more patients on mature follow-up duration. Inclusion criteria for evaluation as stage IIIb were: 1) contralateral mediastinal nodes involved at cervical mediastinoscopy (nodes 2R, 2L, 4R, 4L) or rarely Chamberlain procedure (nodes 5) (mediastinal N3); 2) direct diffuse extension into the mediastinum found at mediastinoscopy and proven by biopsy or recurrent laryngeal nerve palsy (diffuse mediastinal T4); 3) biopsy-proven invasion of the carina (T4 carina); 4) computed tomography (CT)- as well as (MRI)-proven invasion of the spine (T4 spine); 5) invasion of the pulmonary artery proven by angiographic CT scan/MRI (T4 pulmonary artery); and 6) invasion of the superior vena cava proven by angiographic CT scan/MRI or transesophageal endosonography (TEES).

Not eligible for the study were patients with: 1) involved supraclavicular nodes (N3 supraclavicular); 2) esophageal infiltration (T4 esophagus); 3) infiltration of

Table 1. Treatment Schema of Induction CTx Followed by Hf-C/RTx and Surgery

Selected stage IIIB NSCLC (T4, N3)
Initial staging/mediastinoscopy
↓
Induction chemotherapy (CTx)
3 Cycles CIS 60 mg/m^2 days 1 + 7, ETO 150 mg/m^2 days 3–5 qd 22
↓
Induction chemoradiotherapy (Hf-C/RTx)
1 Cycle Cis 50 mg/m^2 days 2 + 9, ETO 100 mg/m^2 days 4–6
TI: 1.5 Gy b.i.d./5 × per week up to 45 Gy days 1–21
(PCI: 2 Gy/day 5 × per week up to 30 Gy days 8–29)
↓
Restaging incl. repeat mediastinoscopy
(only one ipsilateral/no contralateral mediastinal nodes involved)
↓
Surgical resection

b.i.d. = twice daily; CIS = cisplatin; CTx = chemotherapy; ETO = etoposide; Hf-C/RTx = hyperfractionated accelerated chemoradiotherapy; PCI = prophylactic cranial irradiation; SCLC = small cell lung cancer; TI = thoracic irradiation.

aorta thoracica (T4 aorta); 4) ipsilateral satellite pulmonary nodules in the same lobe (T4 satellite nodule); 4) malignant pleural effusion (T4 pleural effusion); and 5) invasion of the myocardium on angiographic CT scan/MRI (T4 myocardium).

To rule out distant metastases, all patients underwent the following staging investigations: CT scans of the chest, abdomen, and brain, radionuclide bone scan, abdominal ultrasound, and physical examination. A complete blood cell count, serum chemistry, coagulation tests, and urinalysis were performed to give normal values. Patients underwent a preoperative cardiovascular risk assesment including cardiopulmonary function testing. Patients were ineligible due to a predicted postoperative forced expiratory volume at 1 s of less than 1 L (quantitative ventilation-perfusion lung scanning), cardiac infarction or unstable angina pectoris 6 months before study entry, or cardiac disability of class III or more (New York Heart Association [NYHA] criteria). Further excluded were patients with: 1) mixed histologies including small cell lung cancer; 2) any other concurrent or previous malignancy; 3) age above 70 years; 4) WHO status greater than 2; and 5) prior oncological treatment (chemotherapy, radiotherapy, surgery). All patients were fully informed about the nature and purpose of this study, and had to give informed consent before study entry. The trial had the local/institutional ethics committee approval. Eligible patients were planned to receive three cycles of induction chemotherapy with split-dose cisplatin and etoposide, followed by one cycle of concurrent hyperfractionated accelerated chemoradiotherapy (Table 1). From 1993 onwards, all patients were routinely offered prophylactic cranial irradiation of 30 Gy in 2-Gy fractions given over 3 weeks (PCI). Patients then were planned for restaging investigations including repeat mediastinoscopy (with biopsies) for those with initially proven positive mediastinal nodes. If reevaluation showed continuing medical/functional operability and repeat mediastinoscopy showed no more than one ipsilateral lymph node station involved (minimal mediastinal disease), patients were taken to thoracotomy 3 to 5 weeks after the end of radiation. Patients still contralaterally involved at repeat mediastinoscopy were generally excluded from surgery. Furthermore, if results of restaging investigations (angiographic CT scans, MRI) clearly indicated persistent T4 disease, thoracotomy was not performed. However, stable disease in N3 patients in spite of mediastinal clearance did not itself render patients ineligible for thoracotomy, nor did biopsy-proven involvement of one single ipsilateral mediastinal lymph node.

All patients who were medically unfit, who showed progressive disease during induction, who had more than one ipsilateral or contralateral lymph node stations still involved at repeat mediastinoscopy even with remission of the primary tumor, or patients who refused any further treatment were not eligible for surgery. These patients received a conventional small-volume tumor boost irradiation to the primary as well as the mediastinum of between 20 and 25 Gy on an individual basis (total dose 65 to 70 Gy).

After treatment completion, follow-up visits were arranged for all patients every 2 months in the first 2 years from the end of treatment and from then on every 3 months. Investigations included physical examination, complete blood cell count and serum chemistry, chest radiographs, and abdominal ultrasound. Bronchoscopy was performed once every year or if relapse was suspected. Follow-up CT scans were only performed if clinically indicated.

Overall survival was calculated from the first day of chemotherapy until death, loss of follow-up, or time of evaluation for this report. Event-free survival was calculated from the first day of chemotherapy until any event such as tumor progression, incidence of second cancer, death due to toxicity, or secondary conditions [12]. Survival curves were estimated by the method of Kaplan and Meier, and differences between the individual curves were evaluated using log-rank test [13, 14]. A forward stepwise Cox regression model was used to examine the prognostic significance of covariates on survival. Significance was accepted if any two-tailed p value was less than 0.05.

Results

From March 1991 until June 1996, 56 patients fulfilling the criteria of IIIb disease (T4 or either N3) non-small cell lung cancer were entered into the complete phase II trial. Three of the patients have been lost to follow-up at 10, 17, and 17 months, because they all moved to other European countries. In the remaining 53 patients, follow-up is complete and known at the date of this evaluation (August 1998). The median follow-up of patients alive at the time of this report is 36 months, with a range between 22 and 88 months.

There were 46 men and 10 women, with a median age

of 55 years (range 34 to 69 years). Median performance status at the time of enrollement into the study was World Health Organization grade 1, with a range between 0 and 2. Median lactate dehydrogenase value was 192 U/L (range 127 to 501). T4 disease criteria were met in 28 patients (50%), whereas N3 nodes were involved in 32 (57%) (four patients with T4N3). Detailed primary tumor, regional lymph nodes, distant metastasis (TNM) stages of the patients and subgroups of T4 disease included in this trial are:

T4N0/1	10
T4N2	14
T4N3	4
T1N3	2
T2N3	17
T3N3	9
T4 subsets	28
T4 pulmonary artery	11
T4 carina	4
T4 spine	3
T4 diffuse mediastinal	9
T4 vena cava	1

None of the patients in the N3 subset had supraclavicular nodes involved, and N3 criteria were met by biopsy-proven positive contralateral mediastinal nodes. Included non-small cell histologies were 29 patients with squamous cell carcinoma (52%), 22 patients with adenocarcinoma (39%), and 5 patients with large cell carcinoma (9%).

During the phase of induction treatment, only 2 patients showed an early progression. In the beginning of the study, 5 patients refused to follow protocol treatment. From 1993 onwards, no patient has refused any treatment planned on protocol. Five patients could not be considered for surgical procedures after induction because of medical reasons (decline in cardiopulmonary functions or performance status), and 1 patient experienced an early death due to septicemia. Due to results of restaging investigations, 9 patients were assessed clinically unresectable, 4 with persistent T4 disease (angiographic CT scans, MRI) and 5 with N3 or more than one N2 level still biopsy-proven positive at repeat mediastinoscopy. Overall, 34 patients underwent a right- or left-sided thoracotomy (61%). The operative procedures in 34 patients taken to thoracotomy included:

Operated	34 of 56 (61%)
Resected	33 of 56 (59%)
Standard resections	(15 of 33)
Lobectomy	8
Bilobectomy	2
Pneumonectomy	5
Complex resections	(18 of 33)
Intrapericardial pneumonectomy	10
Sleeve pneumonectomy	1
Pneumonectomy and chest wall	1
Lobectomy and spine	1
lobectomy and chest wall	2
Sleeve lobectomy	3

All patients were approached by a standard lateral thoracotomy to remove the primary tumor and the ipsilateral mediastinal nodes. Contralateral nodes were generally not resected. From 1993 onwards, the bronchial stump was routinely sutured with 2-0 monofilament, nonabsorbal continuous horizontal mattress suture, that runs the length of the stump. A flap of intercostal muscle or mediastinal fat was used to cover the bronchial stump after right-sided pneumonectomies. The mean intraoperative blood loss was 360 mL (range 110 to 720 mL) and the mean duration of operation was 178 minutes (range 125 to 375 minutes). Twenty-seven patients (48%) had a complete resection performed as far as the pathology results of repeat mediastinoscopy biopsies as well as resected specimen gave information about. Downstaging data available from surgical exploration revealed that 11 of 16 (69%) initially involved N3 nodes, and 5 of 6 (83%) initially involved N2 nodes (T4N2 disease) had become microscopically tumor free after induction, whereas only 8 of 22 (36%) initially evaluated T4 tumors had a pathological complete response. One patient had proven T4 disease at the mediastinum surrounding the vena cava and distal trachea, so that surgery ended as an exploratory thoractomy. Six patients had incomplete resections (R1/R2 in peribronchial tissue in 2, in pericardial margin in 1, and in mediastinal fat in 3 patients) and 3 of them received boost irradiation to the areas of residual disease between 20 and 25 Gy on an individual basis. The other 3 patients refused any further treatment. Deaths during stay in hospital were not observed. One of the 34 patients (2.9%) who underwent thoracotomy died at home 43 days after right-sided lobectomy and carinal resection from massive hemoptysis. Postmortem examination revealed an insufficiency of the tracheobronchial anastomosis and perforation of the pulmonary artery. Seventeen patients did not have any postoperative complication. Complications in the remaining 16 patients included: rethoracotomy for bleeding (2), cardiac arrythmias (4), atelectasis (3), air leakage longer than 7 days (4), pneumonia (1), pleural empyema (1), and nonfatal lung embolism (1). Mean stay in hospital was 11.6 days (range 9 to 26 days).

The actuarial survival rate for all 56 patients entered into the study was 35% at 4 years and 26% at 5 years, with a median survival of 20 months. The corresponding rates were 60% and 43% for the 27 R0 patients, with an overall median survival of 58 months. Seventeen patients with a proven pathological complete response (pCR) had comparable 4- and 5-year survival rates of 75% and 50%, the median survival being 52 months. All 28 patients fulfilling the T4 criteria had 4- and 5-year survival rates of 34% and 17%, and a median survival of 20 months. All 32 patients with mediastinoscopically proven N3 nodes had 4- and 5-year survival rates of 34% and 28%, and a median survival of 20 months. Survival as well as surgical results for the different TN groups are summarized in detail in Table 2. Six patients survived more than 5 years, 4 of them with R0 resection and 2 with pCR. The only subgroup with a tendency, although not statistically significant, to shortened median survival, lower 4- and 5-year survival rates, as well as complete resection and

Table 2. Surgical Results in Different Primary Tumor, Regional Lymph Nodes, Distant Metastasis (TNM) Groups

	T4N0/1 (n = 10)	T4N2 (n = 14)	T1-2N3 (n = 19)	T3-4N3 (n = 13)
Median survival (months)	26.5	20	32	13
4-year survival rate	37.50%	33%	41%	23%
5-year survival rate	37.50%	33%	31%	23%
R0 resection	8/10 (80%)	5/14 (36%)	10/19 (53%)	4/13 (31%)
Pathological complete response	5/10 (50%)	4/14 (29%)	6/19 (32%)	2/13 (15%)

PCR rates was that with combined higher T and N stages of T3N3 and T4N3.

In the group of 27 R0 patients, 1 patient died from a therapy-related complication (anastomosis insufficiency) and 2 patients died from causes not related to treatment or disease (1 patient with lung embolism and 1 with from viral pneumonia 8 and 19 months after completion of treatment). Overall, 12 (44%) have relapsed, 7 with central nervous system (CNS) metastases, 3 with bone metastases, 1 with multiple lung metastases, and only 1 patient locoregionally in the mediastinal nodes. The median event-free survival in all these R0 patients was 52 months, with actuarial rates of 53% at 4 years and 38% at 5 years (Fig 1). In the group of 29 patients in whom complete resection was not part of the initial treatment, 1 patient died from a therapy-related complication (septicemia) and 1 patient was lost to follow-up at 10 months. Twenty-seven (93%) have relapsed. The sites of first relapses were as following: eight in the CNS, two in bone, two in liver; 1 patient combined in bone and brain, 2 both locoregionally, and in the brain and 12 patients locally or locoregionally in the mediastinum. Median event-free survival for the whole group was 10 months, with all patients experiencing their event up to 22 months.

Comment

Standard nonsurgical treatment for stage IIIb disease in non-small cell lung cancer following the revised Mountain classification has shifted from radiotherapy alone to different combinations of chemotherapy and irradiation (sequential, concurrent, altered fractionation), with a significant increase in long-term survivors observed following this bimodality approach, although overall local control is still far from being sufficient [1, 3, 15]. Recent experience has shown that an inclusion of systemic treatment as early as possible into the management of locally advanced non-small cell lung cancer is feasible and effective, with a significant increase of survival in two small randomized trials reported for IIIa [16, 17]. Other investigators have focused on early intensification of preoperative downstaging by so-called "bimodality induction" including chemotherapy as well as radiation therapy before surgery [5–9]. This approach seems to be especially attractive for more locally advanced selected IIIb subgroups, where maximum preoperative downstaging is mandatory to enable complete resection of any vital tumor left after induction, mostly at areas of bulky disease in the primary tumor or the mediastinum. However, it is still not clear which subgroups of stage IIIb do profit from such intensive treatment. Therefore, we must wait for results of the large intergroup trial testing trimodality with inclusion of surgery versus bimodality including definitive chemoradiation for local control [4, 5].

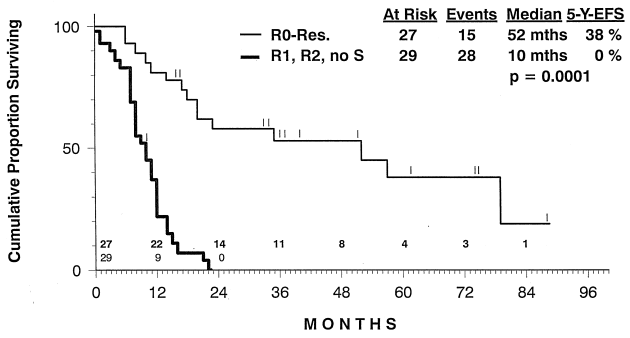

Fig 1. Event-free survival durations in patients with R0 resection versus those with R1, R2 Resection, or no surgery performed (EFS = event-free survival, mths = months, S = surgery).

We have reported here mature follow-up data of 56 IIIb patients entered onto our trimodality protocol from March 1991 through June 1996 at the West German Cancer Center Essen. Sixty-one percent of the patients selected for participation could be operated on, and in 27 (48%), eventually complete resection was performed. Long-term survival at 4 and 5 years of 35% and 26% looks very promising for these advanced-stage subgroups. So far, prognosis of our patients with T4 disease and N3 disease are comparable. Long-term survival became possible in T4N0/1, T4N2, or T1/2N3. The only group with more unfavorable prognosis seems to be the one with higher combined T and N stages (T3N3 and T4N3). This was also the group with the lowest rate of complete resection possible after induction (35%).

The toxicity of this multimodality approach was acceptable (overall mortality 3.6%). We generally used repeat mediastinoscopy (N3) or repeat imaging studies (T4) to select our patients for thoracotomy. We did only operate on those N3 patients in whom initially involved nodes were without evidence for residual cancer postinduction or if not more than one intially involved ipsilateral node remained positive. Further, repeat imaging studies (angiographis CT scan/MRI) had to clearly visualize mediastinal structures without tumor invasion. The rates of intrapericardial pneumonectomies and complex

resections (47%), mostly in T4 tumors, seems adequate for these locally far-advanced stages. In most cases with N3 disease, standard surgical procedures turned out to be sufficient and contralateral mediastinal nodes were not removed. It is still not clear, whether after such an intensive preoperative downstaging the extension of resection can be confined to the primary tumor and the ipsilateral mediastinal nodes or has to include the contralateral mediastinum for achieving an anatomically complete resection of initially involved tissue. Our relapse pattern in the patients with N3 nodes proves that local or locoregional relapse after negative rebiopsies of contralateral nodes is rarely observed. Induction treatment turned out to be much more effective in the mediastinum (69% initially involved N3 nodes free of cancer) than at the primary tumor site (36% pathological complete responses).

The Southwest Oncology Group (SWOG) had some differences in their patient selection as well as in the selection for thoracotomy for the stage IIIB subset. Most of their N3 patients (2/3) had involved supraclavicular nodes, whereas in our trial, this group was generally excluded. The SWOG did not include repeat mediastinoscopy in the postinduction selection for thoracotomy. However, the database of the SWOG did concisively show that N2 or N3 disease at thoracotomy was the most significant negative prognostic factor for postoperative survival duration and prognosis in their patients. Different from our results, the SWOG did find significantly better survival results for the stage subgroup T4N0/1 [4, 5]. Other investigators, Grunenwald and associates from Paris [18] and Choi and associates from Boston [19], have also included IIIb patients into trimodality protocols (T4 as well as N3), comparable with our trial and that of the SWOG [18, 19]. However, in the Boston study, the induction chemoradiotherapy was more intensive with a complex irradiation scheme of combining once- with twice-daily irradiation up to 60 Gy. The Paris trial had comparable radiation doses preoperatively (45 Gy) but included a more complex and extensive surgical approach (sternotomy). They reported a complete resection rate of 57% among 30 patients and a 3-year actuarial survival rate of 25% [18]. Choi and associates found among 26 IIIb patients (T4 or N3) a complete resection rate of 52% and an actuarial 3-year survival of 52% [19].

Some investigators reported a high incidence of bronchopleural fistulas or adult respiratory distress syndrome (ARDS) after induction chemoradiotherapy, especially for pneumonectomies [20]. In our experience, postoperative mortality was low (2.9%), whereas perioperative morbidity seemed to be more pronounced compared with standard operations without pretreatment. However, the rate of bronchopleural fistulas could be reduced, if monofilament, nonabsorbal sutures were used and the bronchial stump was routinely covered with autologous tissue such as intercostal muscle or mediastinal fat. To prevent increased alveolar capillary edema, we routinely administered prophylactic corticosteroids (eg, 1.0 to 1.5 mg/kg/body weight prednisolon) postoperatively for 3 days. Similar to our results, the SWOG, Boston, and Paris trials did not report such high incidences of stump fistulas and ARDS as those observed in Fowler's group [18–20]. It may be that an inclusion of twice-daily radiotherapy is a possible means to shorten radiation duration time and thus leads to decreased evolvement of fibrosis at the time of thoracotomy.

Long-term survival rates now achievable with multimodality treatment with or without surgery for selected IIIb subgroups look very promising if compared with historical controls. This could be partly explained due to selection procedures necessary for these aggressive protocols and, therefore, results of the randomized intergroup trial are urgently awaited. However, if the long-term survival improvement after inclusion of surgery as a definitive local modality would be in the range between 5% and 10% at 5 years for selected subgroups of IIIb, this could easily be missed in one randomized trial alone. Another research priority should be to identify prognostic subgroups of IIIb that definitely profit from such trimodality approaches by including new molecular markers from translational research (eg, K-ras mutations, p53 mutations) into the prognostical analyses.

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DISCUSSION

DR ERINO A. RENDINA (Rome, Italy): I want to congratulate you on a very good experience. I would like to ask you a few questions.

First, why were patients with infiltration of the esophagus and the aorta excluded?

Second, how did you stage these patients? This is a key point in the treatment of T4 lung cancer, and I see that many of your patients were T4.

And then the last question: There are, I think, about 50% of pneumonectomies in your series. Do you think this is inevitable or it can be reduced somehow? Thank you.

DR STAMATIS: We have excluded patients with esophageal infiltration because of the toxicity after irradiation. Transesophageal endosonography was used for evaluation of patients with infiltration of the esophagus and aorta. We think this is a safe and effective method to evaluate T4 tumors in this area. Pneumonectomies were performed for T4 tumors. We have demonstrated that most of the patients with T4 tumors had an infiltration of the great vessels, so that in these cases pneumonectomy was necessary.

DR F. HAMMOND COLE, JR (Memphis, TN): Would you address the issue of repeat mediastinoscopy in group that had chemoradiation. I sort of recoil from that, although people are writing about it. You obviously had no mortality, and I congratulate you on your excellent operative results in this difficult group of patients. What was the yield of nodes on the second mediastinoscopy? Were there any in whom tissue could not be retrieved? And would you just address how you go about this?

Thank you.

DR STAMATIS: Repeat mediastinoscopy is in our hand an accurate method to restage patients with N3 disease after induction therapy. Two things are important. The first one is that repeat mediastinoscopy has to be done by the same surgeon who performed mediastinoscopy. The second one is that biopsies have to be taken from the same nodal stations as by mediastinoscopy. Adhering to these two recommendations, repeat mediastinoscopy is easy to perform. Our present experience with PET is unsatisfactory. We observed 18% of false-positive spots in the mediastinum after induction therapy. The probability is high that these patients could be excluded from surgery.

DR GIUSEPPE CARDILLO (Rome, Italy): Is there a role for videothoracoscopy in restaging these patients and to avoid unnecessary thoracotomy, even if in your study you have done only one exploratory thoracotomy?

DR STAMATIS: We have not used videothoracoscopy because we routinely used the transesophageal endosonography. The fact that only in one case was exploratory thoracotomy necessary showed the accuracy of this method in the evaluation of T4 tumors.

DR NASSER K. ALTORKI (New York, NY): I am just going to take the moderator's prerogative here and make a comment asking what the role of surgery is. I see you operated on 34; 27 had an R0 resection and 16 had a complete pathological CR. So the role of surgery would really hinge on 11 patients here who did not have a complete CR, because you can well argue that those that got a complete pathologic CR did not benefit from the operation.