General Thoracic Surgery

Extended pneumonectomy for non–small cell lung cancer: Morbidity, mortality, and long-term results

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Objective: Pneumonectomy is not always sufficient for the radical resection of cancer. In the present study, pneumonectomy may be associated with an extended resection of mediastinal or parietal structures. The postoperative risk and the oncologic benefits of such an extended procedure have not been sufficiently demonstrated.

Methods: We have defined "extended" pneumonectomy (EP) as the removal of the entire lung, associated with one or more of the following structures: superior vena cava, tracheal carina, left atrium, aorta, chest wall, or diaphragm. Our clinical database was retrospectively reviewed to identify patients who underwent EP to assess their postoperative morbidity, mortality, and long-term survival.

Results: Between 1998 and 2005, 47 EPs were performed. The "extended" procedure included left atrium resection in 15 patients, combined SVC and carinal resection in 9 patients, aortic resection in 8 patients (in 3 patients with prosthetic replacement), chest wall or diaphragmatic resection in 6 patients, SVC resection in 4 patients, and carinal resection in 4 patients. A partial esophageal muscular resection was performed in 1 patient. Overall 60-day mortality was 8.5%. Major postoperative complications occurred in 8 patients (17%). The 2- and 5-year survival rates for the overall population were 42% and 22.8%, respectively. Interestingly, long-term survivors were recorded only in the group of patients who received induction treatment.

Conclusions: Extended pneumonectomy is a feasible procedure with an acceptable risk factor. To improve the selection of patients, all candidates should undergo preoperative mediastinoscopy and induction chemotherapy. In patients with positive response to chemotherapy or stable disease, extended pneumonectomy may afford a radical resection in more than 80% of cases and may result in a permanent cure in some instances.

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Complete tumor removal is the objective of any surgical resection when treating lung cancer.[1] A tumor may infiltrate contiguous structures such as the superior vena cava (SVC), tracheal carina, left atrium, diaphragm, or chest wall. It has been demonstrated that in all of these situations, a radical resection can be achieved by combining an "extended" procedure such as SVC

Abbreviations and Acronyms
ALI   = acute lung injury
ARDS   = acute respiratory distress syndrome
EP   = "extended" pneumonectomy
NSCLC = non–small cell lung cancer
SVC   = superior vena cava
VATS   = video-assisted thoracoscopic surgery

prosthetic replacement, tracheal "sleeve," or left atrium resection with lung surgery, resulting in acceptable morbidity and mortality rates as well as satisfactory long-term results.[2-5]

Of all anatomic resections, pneumonectomy is associated with the highest postoperative mortality rate,[6,7] particularly after induction treatment,[8] and it is often considered a cause of illness in itself, because of its adverse impact on the quality of life of long-term patients. When both an extended procedure and pneumonectomy are required to radically resect a tumor, surgical risk increases and the certainty of oncologic benefits diminishes.

To clarify the role of the extended pneumonectomy in the management of lung cancer patients, we reviewed our patient data (a) to assess the additional risk of extended pneumonectomy as compared with that of standard pneumonectomy in terms of postoperative morbidity and mortality, and (b) to evaluate long-term survival after such an invasive approach.

Materials and Methods

We have defined "extended" pneumonectomy as the removal of the entire lung associated with one or more of the following structures: superior vena cava (SVC), tracheal carina, left atrium, aorta, chest wall, and diaphragm.

The clinical database of the Thoracic Surgery Department of the European Institute of Oncology was reviewed to identify patients who underwent extended pneumonectomy between January 1998 and March 2005. Our Ethical Committee was informed of the study and did not require approval. All patients gave their informed consent for the study.

Preoperative Management

Preoperative work-up consisted of brain, chest, and upper abdomen enhanced CT scan, and bronchoscopic scan. From 2000 on, positron emission tomography was routinely used. Functional evaluation was performed by spirometry, blood gas analysis, and lung perfusion scan. A predicted postoperative FEV1 value of less than 30% was considered a contraindication to pneumonectomy.

Patients having one or more mediastinal lymph nodes with a diameter larger than 1 cm in their short axis on CT scan underwent mediastinoscopy. When N2 disease was detected, they underwent induction chemotherapy in three cycles of cisplatin and gemcitabine (cisplatinum 80 mg/m^2 days 1,21 and gemcitabine 1250 mg/m^2 days 1,8,21) and, in the case of tumor reduction or stable disease,

they underwent surgery. In patients without mediastinal involvement, induction chemotherapy was discussed case by case. The presence of pleural effusion or the clinical suspicion of pleural disease was investigated by video-assisted thoracoscopy in all cases.

Restaging after chemotherapy was performed by brain, chest, and upper abdomen enhanced CT scan and bronchoscopy. The final decision on indication for surgery was taken after multidisciplinary discussion. The delay between the end of chemotherapy and surgery was 4 to 5 weeks.

Postoperative Complications

Postoperative death was defined as any death occurring during hospital stay, or within 30 days after surgery. Sixty-day death was defined as any death occurring within two months from the day of pneumonectomy.

Postoperative complications were classified as: (1) respiratory (acute respiratory failure, ARDS and ALI, as defined by the American European Consensus Conference on ARDS in 1994,[9] pneumonia, sputum retention, pulmonary embolism, pulmonary oedema, chronic respiratory failure), (2) cardiac (cardiac arrythmia, angina, myocardial infarction, cardiogenic shock), (3) surgical (SVC thrombosis, hemothorax, bronchial fistula, empyema, chylothorax, cardiac dislocation), and (4) others. Respiratory, surgical, and cardiac events with the exception of cardiac arrythmia were considered to be major complications. All the others were defined as minor complications.

Intraoperative Management

Intraoperative management was focused on reducing the risk of damage to the controlateral lung; fluid administration was in the order of 5–7ml/kg/hour cristalloids infusion, not exceeding a total amount of 1500 ml in all cases.

In patients requiring SVC resection, intraoperative fluids and vasoactive agents administration was managed differently until SVC replacement was completed. The objective was to obtain a mean arterial pressure before clamping of 80 mmHg, to compensate for the expected drop in arterial pressure at SVC clamping, due to the reduction in cardiac output.[10]

Ventilation was managed using a protective-ventilation strategy (a tidal volume $\leq$ 6ml/kg, driving pressure $<$ 20 cm H20 above the PEEP value, permissive hypercapnia, and the preferential use of pressure-limited ventilatory modes).[11]

The bronchial stump was covered in all cases. Because extended pneumonectomy is often performed intrapericardially, the availabilty of autologous pericardium is often limited and for this reason it was rarely used. The preference was to cover the stump using a pedicled mediastinal fat pad. When it was not available, a pedicled parietal pleura flap was used.

Statistical Analysis

The impact of the following 10 variables on postoperative morbidity was verified (age, sex, induction treatment, preoperative FEV1%, side of pneumonectomy, carinal reconstruction, SVC resection, atrial resection, chest wall resection, and diaphragmatic resection).

Patients were divided into two groups based on the presence or lack of major postoperative complications and were compared for

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Table 1. Clinical characteristics of the study population

Factor	n	%
Males	39	82.9
Age (median)	58.6	
Preoperative chemotherapy	38	80.8
Preoperative FEV1% < 50%	2	4.2
Pathologic condition		
Squamous cell carcinoma	29	61.7
Adenocarcinoma	12	25.5
Large-cell carcinoma	2	4.2
Resection associated with pneumonectomy		
Left atrium resection	15	32
Superior vena cava resection	13	27.6
Carinal resection	13	27.6
SVC + carinal resection	9	19.1
Aorta resection	8	17
Pathologic stage		
Stage I	1	2.1
Stage II	3	6.4
Stage III	43	91.4
Pathologic T< 4	17	36.2
Pathologic T4	30	63.8

all relevant variables using frequency tables for categorical variables and summary statistics for continuous variables. Chi-square or Fisher's exact test were applied when appropriate.

Postoperative complications were considered as outcome variables in a logistic regression model, using the defined covariates. The Odds-ratio and a corresponding 95% of CIs were reported for covariates considered clinically relevant or statistically significant at the 0.05 significance level (Wald chi-square test) and then included in the final multivariate model.

Overall survival and disease-free intervals were estimated from the date of surgery using the Kaplan–Meier survival analysis method. Survival comparisons by stage were analyzed by log–rank test; the difference was considered statistically significant when p-value was less than 0.05.

Follow-up information was obtained via telephone contact on October 2005.

Results

During the period of the present study, 269 pneumonectomies were performed. Forty-seven of them (39 males, mean age 58.6 years) underwent extended pneumonectomies for lung cancer representing the population of the study. Patient characteristics are listed in Table 1.

Thirty-eight patients received preoperative induction chemotherapy. Of the extended procedures associated with pneumonectomy, 15 patients underwent atrium resection (in one patient, this procedure was combined with aortic resection), 9 patients underwent combined SVC and carinal resection, 8 patients underwent aortic resection (in 3 patients with prosthetic replacement, in 1 patient with direct repair, in 4 patients by subadventitial resection), 6 patients under-

went chest wall or diaphragmatic resection (with another extended resection in 2 patients), with 4 patients having SVC resection, 4 patients having carina resection, and 1 patient having partial esophageal muscular resection.

After surgery, postoperative complications occurred in 27 patients (57.4%). Major complications occurred in 8 patients (17%), most of them surgical: 3 early bronchopleural fistulas, 2 hemothoraces, and 1 cardiac herniation, due to pericardial prosthesis rupture. Five major respiratory complications were recorded (10.6%): respiratory failure in 3 cases, ARDS in 1 case, and pulmonary embolism in 1 case. Four patients required temporary tracheostomy for prolonged mechanical ventilation. Univariate analysis did not identify any risk factor for the occurrence of major postoperative complications.

Two postoperative deaths were recorded (overall mortality rate 4.2%) because of ARDS after re-thoracotomy for fistula in one case and simultaneous pulmonary embolism and tracheobronchial fistula in the other. The average ICU was 3 days (range 0–42), with the average hospital stay 10 days (range 5–60). Two subsequent deaths were recorded after discharge, within the 60-day margin: in 1 patient death was due to cardiac failure after left atrium resection, and in 1 patient sudden death occurred at home, with the cause remaining unclear.

A radical resection was obtained in 87% of cases. Final pathologic details are given in Table 1.

Complete follow-up was achieved in all but one patient. 47% of patients were still alive (22/47) at the mean follow-up time of 19 months. Eighteen (38%) were disease free, whereas four had experienced relapse. Out of the 25 recorded deaths, 14 were due to recurrent disease and 11 due to causes unrelated to cancer. In 1 case, the information was not available. Apart from the 4 patients who died within 60 days of surgery, 4 patients died because of respiratory causes, 1 of cardiac causes, 1 of sudden death.

The 2-year and 5-year survival rates for the overall population were 42% and 22.8%, respectively. The overall median survival time was 22 months (95% CI 18–36).

Regardless of the negligible statistical significance, two variables seem to affect long-term survival: lymph node status and type of extended resection. Patients who had mediastinal nodal metastases (N2) had a lower 5-year survival rate (41.2%) compared with those without mediastinal involvement (8.1%, p = 0.13, figure 1). Moreover, patients who underwent carinal resection had a better prognosis as compared with that of those who underwent left atrial resection (34% and 17%, respectively, p > 0.05). Pathologic T status did not affect long-term survival (22% and 26%, respectively, at 5 years for pT < 4 and pT4 tumors, p > 0.5).

It may be interesting to note that long-term survival was obtained only in the group of patients who received induction treatment.

Survival by pN 0,1 vs 2
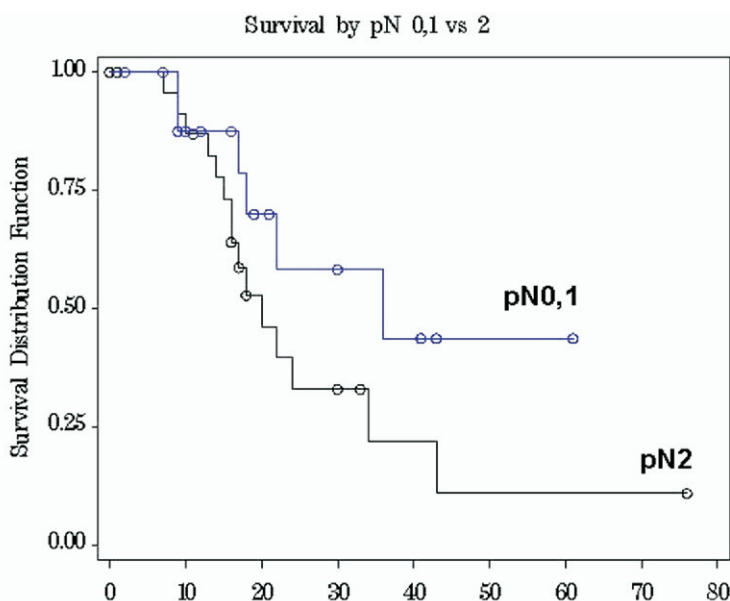
Patients at risk	0	10	20	30	40	50	60
pN0,1	21	12	10	4	2	1	1
pN2	26	20	12	6	2	1	1

Figure 1. Patients who had mediastinal nodal metastases (N2) had a lower 5-year survival rate compared with that of those without mediastinal involvement (N0 and N1, p = 0.13).

Discussion

Lung cancer requiring an "extended" pneumonectomy represents one of the most challenging surgical interventions in oncology, for several reasons.

First, when dealing with patients with suspected mediastinal infiltration, staging of the tumor is extremely difficult because of radiologic inaccuracy.[12,13] This inaccuracy can potentially translate into over-treatment in the cases of SVC, atrial, or carinal resection in "false T4" patients (patients with clinical T4 disease that is not confirmed by pathologic testing), which in our series was in the order of 15%. Moreover, the majority of these patients received chemotherapy before surgery, making the distinction between the response to chemotherapy and an erroneous tumor staging even more problematic.

Second, surgeons who consider clinical T4 tumors as inoperable by definition probably deny permanent cure to a certain proportion of patients. This attitude is not completely justified, given the fact that a T4 tumor can sometimes be radically removed by a tangential SVC[14] or a partial left atrium resection,[15] two procedures that do not increase morbidity and that should be in the repertoire of every thoracic surgeon.

The disadvantage of surgical exploration in clinical T4 patients is that the rate of exploratory thoracotomy is higher. During the study period, we performed 5 exploratory thoracotomies in cT4 patients, mainly due to infiltration of the aortic arch (4 cases), which means unresectable disease in almost 10% of cases. A more extensive use of VATS as a staging tool could probably reduce the rate of exploration in case of suspected aortic infiltration. Morbidity of exploratory thoracotomy when the tumor infiltrates the mediastinum is significant (60% in our experience), because operability can be diagnosed only after extended dissection and intrapericardial vessels isolation. In tumors infiltrating both SVC and the carina, the final judgment on the airways is possible only after SVC resection.

This type of surgery requires highly specialized centers, skilled surgeons, and skilled anesthesists, given the complexity of intraoperative and postoperative management. For example, pneumonectomy requires intraoperative fluid restriction, whereas, at the same time, SVC crossclamping requires generous fluid administration in order to overcome arterial tension drop and the risk of cerebral edema at SVC crossclamping.[10] Anesthesists should be familiar with this problem to reduce the risk of neurologic consequences or early postoperative ARDS.

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Once adequate standard of care is established, maximum attention should be placed on properly selecting patients most likely to benefit from extended pneumonectomy. As previously reported, the most important predictor is mediastinal nodal status,[16,17] the impact of which was suggested but not statistically confirmed in our study because of the small dimension of the population. Patients with persistent mediastinal nodal involvement after chemotherapy have a poor long-term prognosis and should not be considered as candidates for extended pneumonectomy. Given the fact that these tumors are close to the mediastinum, the PET scan is rarely useful for preoperative detection of N2 disease. Consequentially, mediastinoscopy should play a central role in preoperative staging. The best strategy for restaging after chemotherapy remains an open question.

Another debateble argument is the use of preoperative chemotherapy in patients requiring extended surgery. Even in the absence of concrete evidence from literature, we advocate the use of chemotherapy in T4 lung tumors for four main reasons. The first is the clinical observation that a significant proportion of patients who undergo extended surgery develop distant metastases that had not been evident at preoperative staging, after surgery. The second reason is the theoretical advantage of induction treatment (decreasing tumor size, increasing the likelihood of negative margin, sterilizing micro-metastatic disease, defining tumor response to chemotherapy), which may facilitate surgery and exclude patients with rapidly evolving disease. The third consideration is that a negative impact of induction chemotherapy on postoperative mortality has not been clearly demonstrated. Finally, the benefits of chemotherapy in terms of survival have been demonstrated in early stage,[18] stage IIIa,[19,20] and in stage IV.[21] Why should T4 tumors represent an exception? The supposed survival advantage of induction chemotherapy was not evident in our series, and it was instead due to the bias of selection and to the limited dimension of the population. Only a prospective randomized trial could confirm the actual advantages provided by preoperative induction treatment. Unfortunately, its feasibility is limited by several factors, the first being the difficulty of precise clinical staging in T4 tumors.

In our experience, 60-day postoperative mortality after extended pneumonectomy is in the order of 10%, doubled as compared with that of standard pneumonectomy.[22] This increased mortality rate is due to a higher rate of surgical and respiratory complications. In terms of surgical complications, the most dramatically negative event remains bronchopleural fistula, particularly in the case of carinal resection, because no effective salvage repair procedure exists. The increase of respiratory complications is probably linked to preoperative chemotherapy by the mean of Dlco impairement.[23] It is advisable that all candidates for extended pneumonectomy are submitted to Dlco assessment before and after chemotherapy, because patients with a Dlco loss > 20% are probably at higher risk.

From an ethical point of view, is it acceptable to propose a procedure with a 10% postoperative mortality rate? It depends on the alternative, which is chemoradiotherapy with curative intent. Five-year survival after chemoradiotherapy in stage III NSCLC is 3–10%.[24] Our reported surgical survival, comprising R+ patients, was 22%. There is no mean to define whether surgical treatment translates into better cure, but patients are given a chance of permanent cure, which is exceptional by the mean of the other treatment. This is what patients and surgeons want.

This study is limited by 3 factors: its retrospective design, the small number of cases, and the combination of T3 (chest wall and diaphragm) and T4 tumors. The first factor is common to all the other published studies, and it is probably counterbalanced by the fact that our series was collected over a relatively short period of time. Concerning the limited number of patients, as far as we know there are few studies published that focus on the combination of "extended" procedures and pneumonectomy,[25] regardless of the type of extended procedure. As such, we believe that the information available from this series could be useful for further studies. Finally, the decision to consider chest wall or diaphragmatic resections as extended procedures was arbitrary but justified by their morbidity when associated with pneumonectomy. Two of the 4 patients who died within 60 days after surgery underwent such a type of procedure.

In conclusion, "extended" pneumonectomy is a feasible procedure with an acceptable risk. To facilitate an accurate selection of patients, all candidates should undergo preoperative mediastinoscopy (excluding from surgery patients with mediastinal nodal metastases) and induction chemotherapy. In patients with response to chemotherapy, or with stable disease, extended pneumonectomy may afford a radical resection in more than 80% of cases and may result in permanent cure.

References

1. Patterson GA. Extended pulmonary resection: In: Pearson FG, Cooper JD, et al. *Thoracic Surgery*. Vol. 1, 2nd ed. New York: Churchill-Livingstone; 2002, p. 1045-61.
2. Dartevelle PG. Extended operations for the treatment of lung cancer. *Ann Thorac Surg*. 1997;63:12-9.
3. Pitz CCM, De la Riviere AB, Van Swieten HA, Westerman CJJ, Lammers JWJ, Van De Bosch JMM. Results of surgical treatment of T4 non-small cell lung cancer. *Eur J Cardiothorac Surg*. 2003;24:1013-8.
4. Doddoli C, Rollet G, Thomas P, Ghez OP, Seree Y, Giudicelli R, et al. Is lung cancer surgery justified in patients with direct mediastinal invasion? *Eur J Cardiothorac Surg*. 2001;20:339-43.
5. Izbicky JR, Knoefel W, Passlick B, Habekost M, Karg O, Thetter O. Risk analysis and long term survival in patients undergoing extended

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resection of locally advanced lung cancer. *J Thorac Cardiovasc Surg.* 1995;110:386-95.

6. Ginsberg RJ, Hil LD, Eagan RT. Modern thirty day mortality of surgical resections in lung cancer. *J Thorac Cardiovasc Surg.* 1983; 86:654-8.

7. Bernard A, Deschamps C, Allen M, Miller D, Trastek V, Jenkins GD, Pairolero P. Pneumonectomy for malignant disease: factors affecting early morbidity and mortality. *J Thorac Cardiovasc Surg.* 2001;121: 1077-82.

8. Martin J, Ginsberg RJ, Abolhoda A, Bains MS, Downey RJ, Korst RJ et al. Morbidity and mortality after neoadjuvant therapy for lung cancer: the risks of right pneumonectomy. *Ann Thorac Surg.* 2001;72: 1149-54.

9. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med.* 1994;149:818-24.

10. Dartevelle P, Macchiarini P, Chapelier A. Technique of superior vena cava resection and reconstruction. *Chest Surg Clin North Am.* 1995; 5:345-58.

11. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med.* 1998;338:347-54.

12. Di Perna C, Wood DE. Surgical management of T3 and T4 lung cancer. *Clin Cancer Res.* 2005;11:5038s-44s.

13. Cetinkaya E, Turna A, Yldiz P, Dodurgali R, Bedirhan MA, Gurses A, et al. Comparison of clinical and surgical pathologic staging of the patients with non-small cell lung carcinoma. *Eur J Cardiothorac Surg.* 2002;22:1000-5.

14. Spaggiari L, Regnard JF, Magdeleinat P, Jauffret B, Puyo B, Levasseur P. Extended resections for bronchogenic carcinoma invading the superior vena cava system. *Ann Thorac Surg.* 2000;69:233-6.

15. Ratto GB, Costa R, Vassallo G, Alloisio A, Manieri P, Bruzzi P. Twelve-year experience with left atrial resection in the treatment of non-small-cell lung cancer. *Ann Thorac Surg.* 2004;78:234-7.

16. Regnard JF, Perotin C, Giovanetti R, Sschussler O, Petino A, Spaggiari L, et al. Resection for tumor with carenal involvement: technical aspects, results and prognostic factors. *Ann Thorac Surg.* 2005;80: 1841-6.

17. Suzuki K, Asamura H, Watanabe S, Tsuchiya R. Combined resection of superior vena cava for lung carcinoma: prognostic significance of patterns of superior vena cava invasion. *Ann Thorac Surg.* 2004;78: 1184-9.

18. Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, et al. Vinorelbine plus cisplatin vs. observation in resected non–small-cell lung cancer. *N Engl J Med.* 2005;352:2589-97.

19. Rosell R, Gomez-Codina J, Camps C, Maestre J, Padille J, Canto A, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med.* 1994;330:153.

20. Roth JA, Fossella F, Komaki R, Ryan MB, Putnam JB Jr, Lee JS, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *J Natl Cancer Inst.* 1994;86:673.

21. The Elderly Lung Cancer Vinorelbine Italian Study Group. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. *J Natl Cancer Inst.* 1999;91:66.

22. Leo F, Solli P, Veronesi G, Radice D, Floridi A, Gasparri R et al. Does chemotherapy increase the risk of respiratory complications after pneumonectomy? *J Thorac Cardiovasc Surg.* 2006;132:519-23.

23. Leo F, Solli P, Spaggiari L, Veronesi G, De Braud F, Leon ME, et al. Respiratory function changes after chemotherapy: an additional risk for post-operative respiratory complication? *Ann Thorac Surg.* 2004; 77:260-5.

24. Marino P, Preatoni A, Cantoni A. Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stage IIIa and IIIb non-small cell lung cancer. A meta-analysis. *Cancer.* 1995; 76:593-601.

25. Dyszkiewicz W, Piwkowski C, Kasprzyk M, Ramlau R, Adamczak J, Pawlak K. Extended pneumonectomy for non small cell lung cancer: should we still do it? *Neoplasm.* 2004;51:150-4.

Discussion

Dr Wood. Dr. Veronesi, congratulations on very good work by you and your group on a complex group of patients. These are difficult patients, and you certainly got good results both in operative outcomes as well as in survival in a group of patients with advanced disease.

I wanted to emphasize a couple of points that were more in your paper than in the presentation. One was this aspect of clinical overstaging of T4 disease. In your series you found it 15% of the time. There is a series from about four years ago in the European Journal of Cardiothoracic Surgery that found clinical overstaging of T4 disease 40% of the time. I think that it is important to emphasize this experience since often a thoracic surgeon will not see these patients because they are clinically staged as T4 and felt to be unresectable. Or we may see them and deny surgical consideration for the same reason, yet they may really have T2-3 disease due to overstaging. This is one important aspect of looking at patients with locally advanced disease.

My first question is whether you think there really is a difference between T3 and T4 disease. You said that was a limitation of your study, but is there biologically any reason that there is a difference between T3 disease and T4 disease, and should we treat them any differently if we can achieve a complete resection?

Dr Veronesi. When I say limitation of the study, I mean that the group of chest wall resection and diaphragm resection doesn't reach the common definition of extended resections in literature definition. Nevertheless, I put this kind of patient in the work because we found that after pneumonectomy they also have a high rate of complications, so I think very aggressive surgery even in this case is T3 and T4, T3 diaphragm or chest wall. We included it for this reason, but the biologic difference I think is not so high, because in both cases I suggest induction chemotherapy. It may be that downstaging after chemotherapy may make a T4 become a T3 after surgical exploration.

Dr Wood. This is another place where we can educate our medical colleagues that we work with because they often consider T4 to be a contraindication to surgery and biologically the differentiation is arbitrary. It is arbitrary, based upon a historical surgical definition of what we can resect or not, and that is changing.

Your conclusions emphasized the importance of mediastinal staging and I couldn't agree with you more. The principles of success in lung cancer surgery are completeness of resection, which is more difficult in this group of patients, and nodal status. It does appear that if these patients also have advanced nodal status then they probably are not going to benefit from surgery. I agree completely with you in that regard.

I would respectfully disagree with you about the role of induction chemotherapy. Most of your patients had induction chemotherapy, which prevents you from being able to really compare the impact of not having induction chemotherapy or having it. The purported benefits are trying to decrease the extent of resection or improve resectability with negative margins and to treat potential systemic disease. These patients do need systemic therapy at some point in their treatment but not necessarily before surgery. Chemotherapy does create the problem of figuring out where the

margins should be because of the chemotherapy response around tumor. You also made the point that induction therapy increases morbidity and mortality in pneumonectomy, so I guess I would challenge you and question: do you really think that we should give these patients chemotherapy? We do not have strong evidence that it increases resectability. We do have strong evidence that it increases morbidity and mortality. Should we reconsider this conclusion from your paper?

Dr Veronesi. In another work we are going to publish, we found that induction chemotherapy increased morbidity but finally not mortality in pneumonectomy, so we had more than 50 pneumonectomies after chemotherapy. The other observation I can make is the few long-term survivals in this series had all received induction chemotherapy. I know that it is not significant from a statistical point of view but it is an observation.

Dr Wood. Yes, but all but nine of your patients had induction chemotherapy, so it would be hard for it to be otherwise.

Dr Veronesi. The fact that . . . (end of cassette)

Dr Wood. We recommend mediastinoscopy in all of these patients, not only for identifying nodal disease, but also for minimally invasive exploration of the mediastinum. Mediastinoscopy can help determine the extent of airway involvement or the extent of pulmonary artery involvement before committing the patient to a thoracotomy, as well as developing some of the tissue planes that are subsequently useful when you are doing a carinal resection. Are you doing mediastinoscopy at the time of the planned resection and do you find that same benefit in terms of staging the mediastinum not just for nodes but for extent of primary tumor?

Dr Veronesi. Not particularly. We use it mostly for nodal staging and when not positive we perform induction chemotherapy and then we don't perform a redo-mediastinoscopy, so usually it is a long period in advance compared with the surgery.

Dr Wood. Congratulations again on your work. Very nice presentation and nice paper. Thank you.

Dr Veronesi. Thank you.

Doctor [unidentified]. Thank you so much for giving me the opportunity to raise some questions. It was a fine presentation, but for me there remain three questions. The first one, you mentioned the combination of T3 and T4 patients is a weak point of your presentation. Why didn't you exclude T3 patients who have, as we all know, the much better prognosis? The second question is, you mentioned four T1 cases. How _____ to explain? And the third one, there begins really the atrial resection: all intrapericardial resections or where is exactly the border?

Dr Veronesi. I'll start with your final question. The resection was defined as resection not of the vein but of the wall of the atrium at the pathologic exam, so the muscle layer was present. I couldn't understand your second question, sorry. Could you repeat it?

Doctor [unidentified]. The second question is, you made a table with 4 cases in stage T1.

Dr Veronesi. One case. There was 1 case of stage T1.

Doctor [unidentified]. Why do you do an extended pneumonectomy for T1?

Dr Veronesi. It was a case that had a major response to chemotherapy, so we couldn't know the tissue viability before the surgery.

And the first question about T3 and T4, we discussed before with Dr. Wood.

Doctor [unidentified]. Yes, but T3 is quite another entity from T4. If you mix it, you ameliorate the prognosis of the patients of the _____ group. I don't know whether it is correct or not.

Dr Veronesi. Yes, but maybe some T3 were T4 before induction chemotherapy, so we never know that.

Dr Doty. I was taken by the sentence in the abstract, "Neither postoperative outcome nor survival were significantly influenced by the type of extended pneumonectomy." Just to give you a little perspective on this, my first experience over 40 years ago with the pneumonectomy was with the late George Lindesmith, and it was a large bronchogenic carcinoma originating in the right main bronchus deep in the mediastinum. I was really determined to have the opportunity to resect that lung, and George Lindesmith said to me, "You know, Don, getting out a lung cancer is always possible. It just depends on how hard you want to work, but it won't make any difference in the end." And so here we are with 23% survival in extended pneumonectomies 40 years later. It's kind of the same, isn't it? I mean have we really made any progress on this? I just leave you to answer that question. You don't have to. You're too young.

Dr Mulligan. Perhaps a question for the group to reflect upon.