Pneumonectomy is a valuable treatment option after neoadjuvant therapy for stage III non–small-cell lung cancer

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Objective: The mortality of pneumonectomy after chemotherapy or chemoradiotherapy for locally advanced non–small-cell lung cancer is reported to be as high as 26%. We retrospectively reviewed the medical records of patients undergoing these procedures in 2 specialized thoracic centers to determine the outcome.

Methods: Retrospective analyses were performed of all patients who underwent pneumonectomy after neoadjuvant chemotherapy or chemoradiotherapy for locally advanced non–small-cell lung cancer from 1998 to 2007. Presurgical treatment consisted of 3–4 platin-based doublets alone in 20% of patients or combined with radiotherapy (45Gy) to the tumor and mediastinum in 80% of patients.

Results: Of 827 patients who underwent neoadjuvant therapy, 176 pneumonectomies were performed, including 138 (78%) extended resections. Post-induction pathologic stages were 0 in 36 patients (21%), I in 33 patients (19%), II in 38 patients (21%), III in 57 patients (32%), and IV in 12 patients (7%). Three patients died of pulmonary embolism, 2 patients of respiratory failure, and 1 patient of cardiac failure, resulting in a 90 postoperative day mortality rate of 3%; 23 major complications occurred in 22 patients (13%). For the overall population, 3-year survival was 43% and 5-year survival was 38%.

Conclusion: Pneumonectomy after neoadjuvant therapy for non–small-cell lung cancer can be performed with a perioperative mortality rate of 3%. Thus, the need of a pneumonectomy for complete resection alone should not be a reason to exclude patients from a potentially curative procedure if done in an experienced center. The 5-year survival of 38%, which can be achieved, justifies extended surgery within a multimodality concept for selected patients with locally advanced non–small-cell lung cancer. (*J Thorac Cardiovasc Surg* 2010;139:1424–30)

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Despite the fact that more than one third of all patients with non–small-cell lung cancer (NSCLC) present with stage III disease at the time of diagnosis, there remain controversies about treatment recommendations for these patients. Many centers treat patients with locally advanced disease with palliative intent or chemoradiotherapy only and exclude surgi-

cal resections, especially if a pneumonectomy would be necessary for complete resection.

Since the 1990s, neoadjuvant therapy, in particular preoperative chemotherapy, has been increasingly used for stage III NSCLC to downstage tumors, to render them completely resectable, and to possibly eradicate lymph node metastasis in the mediastinum.¹ Several smaller randomized studies have reported survival benefits from neoadjuvant chemotherapy followed by surgery compared with surgery alone.^{1,2} To further improve local control of the tumor and to clear the mediastinum from lymph node metastasis, chemotherapy has also been combined with radiotherapy of the tumor and mediastinum. However, this was associated with a higher risk of intraoperative and postoperative complications, and the best way to combine chemotherapy and radiotherapy has not been determined.^{3,4} Some series have reported an increase of morbidity from 20% to 60% and an exceedingly high perioperative mortality of up to 26% when pneumonectomy was performed, especially on the right side.^{5–7} This led to the conclusion by some authors that pneumonectomy after neoadjuvant chemotherapy or chemoradiotherapy should be avoided in all cases. However, such dismal outcomes are not observed by all, and some smaller studies reported even no perioperative deaths in patients who underwent pneumonectomy after chemoradiotherapy.^{4,5}

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Disclosures: None.

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Received for publication May 13, 2009; revisions received Jan 27, 2010; accepted for publication Feb 20, 2010; available ahead of print April 26, 2010.

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0022-5223/\$36.00

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doi:10.1016/j.jtcvs.2010.02.039

Abbreviations and Acronyms

- ARDS = acute respiratory distress syndrome
- BPF = bronchopleural fistula
- CT = computed tomography
- HR = hazard ratio
- NSCLC = non–small-cell lung cancer
- PET = positron emission tomography

Therefore, in this 2-center study, we retrospectively reviewed the perioperative mortality, morbidity, and outcome of pneumonectomies performed after neoadjuvant chemotherapy or chemoradiotherapy in patients with locally advanced NSCLC.

MATERIALS AND METHODS

A retrospective analysis on patients with locally advanced NSCLC who were treated from 1998 to 2007 with neoadjuvant chemotherapy or chemoradiotherapy followed by pneumonectomy at the Ruhrlandklinik, Essen-Heidhausen, Germany, and the University Hospital Zurich, Zurich, Switzerland, was performed. Data were collected from the clinical charts, operating reports, and pathology reports, and survival data were retrieved from the institutional lung cancer follow-up registry. Follow-up was complete in all patients. Permission to perform such an outcome analysis was included in the informed consents before surgery.

In the time period chosen, 827 patients with potentially resectable clinical T4, N2, or N3 NSCLC underwent neoadjuvant therapy followed by surgery. Pneumonectomies were performed in 176 patients; this cohort formed the basis of our analysis. The median age at time of surgery was 56 years (range, 33–74 years), and 122 of 176 patients (69%) were male. Neoadjuvant chemotherapy consisted of 3 to 4 cycles of platin-based doublets. Patients treated with neoadjuvant chemoradiotherapy received 45 Gy (1.5 Gy, bi-daily) to the primary tumor and mediastinal lymph nodes. In patients who received radiotherapy in Essen, an additional cycle of platin-based doublets was added. Treatment regimens were applied according to different treatment protocols that changed over time in the 2 institutions.

Tumors were classified and staged according to the 1997 International System for Staging of Lung Cancer.⁸ Staging and restaging were routinely performed with computed tomography (CT) of the chest and upper abdomen, and mediastinoscopy or, more recently, endobronchial ultrasound-guided fine-needle aspiration. Mediastinal lymph node involvement was confirmed by histology or cytology. Additional staging tests, such as positron emission tomography integrated (PET) in CT, brain CT/magnetic resonance imaging, and bone scintigraphy, were used according to local protocols and clinical signs and symptoms. T4 tumors in our series included local invasion only. Patients with 2 lesions in 1 lobe or malignant pleural effusion were excluded. Patients were selected for surgery when complete resection was expected on the basis of the preoperative evaluation of the CT or PET/CT scan and when the pulmonary reserve of the patient was sufficient without relevant cardiac or other comorbidities. If necessary, physiologic eligibility for pneumonectomy was assessed with 99mTc lung perfusion scintigraphy to better predict postoperative lung function. Patients with an objective response or at least stable disease after neoadjuvant therapy were primarily, but not exclusively, selected for surgery.

Pneumonectomies were performed using similar techniques within both centers. An anterolateral thoracotomy in the fourth or fifth intercostal space was performed. Staplers were used for closing the pulmonary arteries, pulmonary veins, and main bronchus in most cases. The right and left bronchial stumps were regularly covered with a pericardial fat pad in Essen and irreg-

TABLE 1. Repartition of preinduction clinical stages

	Total	cTNM	n
IIB	8	T2N1	8
IIIA	72	T3N1	1
		T1-3N2	71
IIIB	94	T4N0-2	67
		T4N3	13
		T1-3N3	14
IV	2	M1 (BRA)	2

ularly in Zurich with a pericardial fat pad, an intercostal muscle flap, or nothing. In cases of local invasion, additional structures, such as pericardium (intrapericardial resection), vena cava, aorta, trachea, and others, were resected to get clear margins. A lymphadenectomy of the mediastinal lymph nodes, performed according to the European Society of Thoracic Surgeons guidelines, was an integral part of the procedure.⁹ One chest tube without suction was placed in the chest and removed within 24 hours if no significant bleeding was present. Patients were kept in the intermediate or intensive care unit for 24 hours postoperatively or according to clinical needs before discharged to the ward.

Few patients received further postoperative therapy. This included 3 patients with incomplete resection who received postoperative radiotherapy to the local site and 4 patients with persisting N2 disease who received radiotherapy to the mediastinum.

Statistical analysis was performed using patched SPSS 16.0 for Windows software (SPSS Inc, Chicago, Ill). Univariate logistic regression was used to assess the impact of relevant variables on the incidence of postoperative complications. Age, type of induction therapy, and side and type of pneumonectomy were used to assess the incidence of major postoperative complications, and type of induction therapy, presence of tracheal sleeve resection, and side of pneumonectomy were used to assess the incidence of bronchopleural fistula (BPF). Overall survival was estimated from the date of surgery using the Kaplan–Meier survival analysis method. The impact on survival of 14 variables—age, gender, preinduction clinical stage, preinduction clinical T, N, M status, type of induction therapy, tumor histology, type of operation, postinduction pathologic stage, postinduction pathologic T, N, M status, and R-resection status—were assessed by Cox regression for continuous and log-rank test or Breslow test when necessary for discrete variables. Variables with statistic significance were further analyzed in a multiple Cox regression model (forward/backward).

RESULTS

From 1998 to 2007, 176 patients underwent a pneumonectomy after neoadjuvant chemotherapy or chemoradiotherapy for locally advanced NSCLC, representing 21% of the resections treated with such a combined approach.

Neoadjuvant chemotherapy alone was administered in 35 patients (20%), and neoadjuvant chemoradiotherapy was administered in 141 patients (80%). At diagnosis, 8 patients were classified as stage IIB, 72 patients were classified as stage IIIA, 94 patients were classified as stage IIIB, and 2 patients were classified as stage IV with solitary brain metastasis (Table 1). N2/N3 was pathologically proven by cytology or histology. Complete response was recorded in 36 patients (21%), all having received chemoradiotherapy (Figure 1).

Of 176 pneumonectomies, 86 (49%) were right-sided and 138 (78%) were extended because of additional resections. This is summarized in Table 2. R0 resection was

FIGURE 1. Response to induction therapy.

documented in 162 patients (92%); the remaining patients had R1 or R2 resection.

Histology was squamous cell carcinoma in 101 patients (57%), adenocarcinoma in 46 patients (26%), large cell carcinoma in 17 patients (10%), and not otherwise specified in 12 patients (7%).

Postoperative 90-day mortality was 3%. Three patients died of pulmonary embolism, 2 patients died of respiratory failure (pneumonia/acute respiratory distress syndrome [ARDS]), and 1 patient died of cardiac failure. Within 90 postoperative days, 23 major complications occurred in 22 patients (13%): Six patients had pneumonia/ARDS, 5 patients had BPF, 5 patients had empyema without BPF, 3 patients had pulmonary embolism, 2 patients had hemothorax necessitating reoperation, 1 patient had heart failure, and 1 patient had gastric herniation caused by technical failure of the diaphragmatic repair.

Univariate logistic regression showed that patients with induction chemoradiotherapy had fewer major postoperative complications than patients with chemotherapy alone ($P = .024$, odds ratio = 0.344). Univariate logistic regression

for variables such as age ($P = .171$), side of pneumonectomy ($P = .155$), and type of operation ($P = .081$) failed to show an influence on major morbidity. BPF occurred in 3 covered stumps (2 right and 1 left pneumonectomies) and 2 uncovered stumps (all right pneumonectomies). Univariate logistic regression did not show any statistically significant impact of the type of induction treatment ($P = .272$), the presence of tracheal sleeve resection ($P = .999$), or the side of pneumonectomy ($P = .193$) on BPF occurrence.

The median survival of all patients was 23 months; 3- and 5-year survivals were 43% and 38%, respectively (Figure 2). Univariate and multiple Cox regression models identified 6 and 3 statistically significant predictors for survival,

TABLE 2. Type of resection associated with extended pneumonectomies after induction treatment

Type of resection	n	%
Pericardium	112	81
Left atrium	28	20
Parietal pleura	24	17
Trachea/carina	9	7
Chest wall	8	6
Superior vena cava	8	6
Pulmonary artery truncus	8	6
Diaphragm	7	5
Aorta	4	3
Esophageal wall	3	2

FIGURE 2. Overall survival after induction therapy and pneumonectomy for NSCLC.

TABLE 3. Identification of survival predictors in univariate and multiple Cox regression analyses

Covariates	β	P value	HR	95% CI
Univariate analysis				
Age		.361*		
Gender		.361†		
cStage		.592†		
cT status		.793†		
cN status	0.3	.007*	1.4	1.1–1.8
cM status		.886†		
Type of neoadjuvant treatment		.062†		
Histology				
SC vs AD	0.7	.002*	2.0	1.3–3.1
SC vs LC	1.1	<.001*	3.1	1.7–5.7
SC vs other		.101*		
Type of operation		.558†		
ypStage	0.1	<.001*	1.0	1.0–1.1
ypT status		.071†		
ypN status	0.3	.003*	1.4	1.1–1.7
ypM status	1.2	<.001*	3.2	1.8–5.7
R-resection	0.8	.008*	2.3	1.2–4.4
Multiple Cox analysis				
Histology				
SC vs AD	0.5	.027*	1.7	1.1–2.6
SC vs LC	1.1	.001*	2.9	1.5–5.4
SC vs other	0.7	.097*	1.9	0.9–4.0
R-resection	0.9	.012*	2.3	1.2–4.6
cN status	0.2	.073*	1.2	1.0–1.6
ypM status	0.8	.032*	2.1	1.1–4.3

HR, Hazard ratio; CI, confidence interval; SC, squamous cell carcinoma; AD, adenocarcinoma; LC, large cell carcinoma. β = coefficient. *P values were derived from the Cox regression analysis. †P values were derived from the log-rank or Breslow tests when necessary.

respectively. These P values, hazard ratios (HRs), and their respective 95% confidence intervals are summarized in Table 3.

There was no difference in survival between patients presenting with stage IIIA and patients presenting with stage IIIB ($P = .669$ (Figure 3). Survival for stages IIIA and IIIB was further analyzed according to patients' T and N status (Figure 4). No statistical significance in survival among stages IIIA (T1-3N2), IIIB (T4N0-2), IIIB (T1-3N3), and IIIB (T4N3) was demonstrated ($P = .660$).

Figure 5 shows survival according to pathologic stage at surgery after neoadjuvant therapy. The best survival was found for patients with complete response after neoadjuvant therapy, who had a 5-year survival of 56%. Patients downgraded to stages I and II had a 5-year survival of 35% and 34%, respectively. Patients with persisting stage III disease had a 5-year survival of 31%, whereas all patients with stage IV disease documented at surgery died within 3 years.

DISCUSSION

The treatment of patients with locally advanced NSCLC remains a challenge and is discussed controversially. In gen-

FIGURE 3. Survivals for locally advanced preinduction clinical stages IIIA and IIIB NSCLC.

eral, patients benefit from surgery, when a radical resection can be achieved with a low morbidity and mortality. Although there is consensus about the indication for a multimodality approach in most patients with locally advanced disease, there is no clear agreement about which local therapy should be applied in a given situation.

Recent studies suggested missing benefits, as well as unacceptable high morbidity and mortality, for patients with locally advanced NSCLC treated by resection after neoadjuvant therapy. The European Organisation for Research and Treatment of Cancer trial published by Van Meerbeek and colleagues¹⁰ reported similar survival after surgery or radiotherapy after neoadjuvant chemotherapy in 154 patients with stage IIIA N2 disease judged to be primarily unresectable.

FIGURE 4. Survival for preinduction clinical stages IIIA and IIIB, according to their T and N status.

FIGURE 5. Stage-related survival after induction therapy and pneumonectomy for NSCLC.

However, the rate of incomplete resection remained more than 50% after neoadjuvant therapy, and therefore the lack of a survival advantage in the surgical arm should not be interpreted as a surprise. Nevertheless, patients with complete resection reached a 27% 5-year survival compared with an overall 5-year survival of 15.7% in the surgery arm and 14% in the radiation arm. This confirms once again that only a complete resection has a positive impact on survival and that incomplete resection is comparable to radiotherapy.

The heterogeneity of stage III NSCLC and the variability of definitions of what constitutes resectable disease among different surgeons make it difficult to state general rules as to the applicability of surgery. The clinical extremes toward resectability, a diseased single nodal station not adherent to a vital structure versus multilevel bulky and confluent lymph nodes, are easily recognized. But there is a grey zone in between where imaging techniques and definitions count, but also clinical experience. This is specifically a dilemma because patient selection is of paramount importance. The univariate ($P = .037$, HR = 1.4), but not the multiple ($P = .073$), analysis confirmed the importance of clinical N-status at presentation on survival. Furthermore, our study reconfirms that good responders to neoadjuvant chemotherapy or chemoradiotherapy have a better survival. Pathologic stage at surgery ($P < .001$, HR = 1.0), N status ($P = .003$, HR = 1.4), and M status ($P < .001$, HR = 3.2) were significant predictors of survival in a univariate analysis; M status ($P = .032$, HR = 2.1) was confirmed in the multiple analysis.

Differences in clinical staging procedures and inclusion criteria for neoadjuvant therapy, as well as the presence of small patient cohort studies, render the comparison of long-term survival among studies difficult. Five-year survival after neoadjuvant therapy for stage III disease was reported between 30% and 40%.¹¹⁻¹³ One small recent study with 35

pneumonectomies after neoadjuvant treatment in patients with clinical preoperative stage IIIA “minimal N2 disease” (with a maximum of 2 positive mediastinal lymph node stations and no extranodal growth) and T4N0M0 disease reported an encouraging 5-year survival of 46%.⁴ In our experience with a high proportion of stage IIIB disease, the 5-year survival was 38%. This excellent survival could be explained by various components, such as a high complete resection rate with a low perioperative mortality, a high remission rate after chemoradiotherapy (21%), and an accurate selection of patients for surgery via an efficient staging/restaging process with PET/CT, mediastinoscopy, or endobronchial ultrasound-guided fine-needle aspiration.

Not surprisingly, squamous cell carcinoma appeared in the univariate and multiple analyses as a statistically significant favorable histology regarding survival compared with adenocarcinoma ($P = .002$, HR = 2.0 and $P = .027$, HR = 1.7) and large cell carcinoma ($P < .001$, HR = 3.1 and $P = .001$, HR = 2.9).

As shown in many studies, R0 resections had a favorable impact on survival, compared with incomplete resections in univariate analysis ($P = .008$, HR = 2.3) and multiple ($P = .012$, HR = 2.3) analyses.

Albain and colleagues¹⁴ recently reported the results of a phase III controlled randomized trial of radiotherapy plus chemotherapy with or without surgical resection in 396 patients with stage IIIA N2 NSCLC. No survival difference was shown between the surgical and nonsurgical arms. A closer look at this study, however, shows that the mortality rate for patients after pneumonectomy was as high as 26%. Patients who received a lobectomy after chemoradiotherapy and without such exceedingly high perioperative mortality had a clear survival benefit compared with a matched control group.

The high mortality rate of pneumonectomies after neoadjuvant therapy reported in this randomized study and the high rate of incomplete resection described in the other randomized study from Van Meerbeek and colleagues¹⁰ differed markedly from the perception we had from our own experience and prompted us to perform this retrospective analysis of patients undergoing pneumonectomy after neoadjuvant chemotherapy or chemoradiotherapy.

Within pulmonary resections, pneumonectomy has been associated with the highest morbidity and mortality of all elective thoracic surgical procedures. Without neoadjuvant treatment, mortality after pneumonectomy has been reported between 1.6% and 13.4%.^{15,16}

Even recent reviews note that neoadjuvant treatment, especially chemoradiotherapy, increases the risk of postoperative complications and deaths.¹⁷ Preoperative high-dose radiotherapy (>45 Gy) proved to be a significant risk factor for postoperative complications in several studies.^{6,7}

In our study, neoadjuvant chemotherapy and chemoradiotherapy were given in 35 and 141 patients, respectively, and followed by mostly extended pneumonectomies with

a postoperative mortality rate of 3%. Some smaller studies showed comparable results for pneumonectomy after neoadjuvant chemotherapy, with death rates reaching less than 7.5%.^{11,18} The use of radiotherapy (45 Gy) as component of the neoadjuvant treatment¹⁹ did not increase the rate of complications or mortality in our study. This favorable outcome may be the result of a careful patient selection for pneumonectomy taking into account performance status, pulmonary and cardiovascular function tests, and the extensive surgical and anesthesiologic experience available in the centers participating in this analysis. Although most of the pneumonectomies were extended resections, major morbidity occurred in only 13% of patients. The comparison of overall morbidity rates between studies is difficult because of varying definitions of postoperative complications. Complication rates in our study were 3.4% for pneumonia/ARDS, 2.8% for post-pneumonectomy empyema without bronchus stump insufficiency, and 2.8% for bronchus stump insufficiency. Our morbidity rates are among the lowest when compared with reports of the literature. For example, postoperative ARDS has been reported between 1.8% and 46%, with higher rates observed in particular after neoadjuvant chemoradiotherapy.^{3,7,11,20,21} The rate of pneumonia varies in the literature from 3% to 19%.^{11,20-23} The rate of empyema reported after neoadjuvant therapy ranged from 1.3% to 7.4%.^{3,20,21} Bronchus stump insufficiency after neoadjuvant therapy and pneumonectomy was reported between 0% and 14%, including a higher risk after right-sided procedures.^{3,7,11,18} The increased frequency of bronchus stump insufficiency on the right side is well known and explained by the fact that the right stump is more exposed in the pleural space and less naturally buttressed by mediastinal structures. Bronchial stump-covering techniques have been proven as highly effective procedures to prevent BPF.²⁴ In our institutions, bronchial stumps after neoadjuvant therapy are covered whenever possible with pre-pericardial fat pad or intercostal muscle. Bronchus stump insufficiency occurred in 3 covered stumps (1 left and 2 right pneumonectomies) and 2 uncovered stumps (all right pneumonectomies). Univariate logistic regression failed to show an influence of the type of induction treatment ($P = .272$), the presence of tracheal sleeve resection ($P = .999$), or the side of pneumonectomy ($P = .193$) on BPF occurrence (data not shown).

CONCLUSIONS

The results of our retrospective analysis demonstrate that pneumonectomy after neoadjuvant chemotherapy or chemoradiotherapy with 45 Gy for locally advanced stage IIIA and IIIB NSCLC can be performed safely with a mortality rate of 3%, a 90-day major morbidity of 13%, and an encouraging overall 5-year survival of 38%. The importance of sufficient hospital volume on the surgical outcome of such complex procedures has also been highlighted.²⁵ These results chal-

lenge any surgical nihilism for patients with locally advanced NSCLC and emphasizes that surgery, when performed in experienced centers, continues to have an important role within the multimodality therapy of these patients.

References

- Rosell R, Gomez-Codina J, Camps C, Maestre J, Padille J, Canot 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; 330:153-8.
- 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: 673-80.
- 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.
- Gudbjartsson T, Gyllstedt E, Pikwer A, Jönsson P. Early surgical results after pneumonectomy for non-small cell lung cancer are not affected by preoperative radiotherapy and chemotherapy. *Ann Thorac Surg*. 2008;86:376-82.
- Sonet JR, Suntharalingam M, Edelman MJ, Patel AB, Gamliel Z, Doyle A, et al. Pulmonary resection after curative intent radiotherapy (>59 Gy) and concurrent chemotherapy in non-small cell lung cancer. *Ann Thorac Surg*. 2004;78:1200-5.
- Deutsch M, Crawford J, Leopold K, Wolfe W, Foster W, Herndon J, et al. Phase II study of neoadjuvant chemotherapy and radiation therapy with thoracotomy in the treatment of clinically staged IIIA non-small cell lung cancer. *Cancer*. 1994;74: 1243-52.
- Fowler WC, Langer CJ, Curran WJ Jr, Keller SM. Postoperative complications after combined neoadjuvant treatment of lung cancer. *Ann Thorac Surg*. 1993; 55:986-9.
- Brambilla E, Travis WD, Colby TV, Corrin B, Shimosato Y. The new World Health Organization classification of lung tumours. *Eur Respir J*. 2001;18: 1059-68.
- Lardinois D, De Leyn P, Van Schil P, Rami-Porta R, Waller D, Passlick B, et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. *Eur J Cardiothorac Surg*. 2006;30:787-92.
- Van Meerbeek JP, Kramer GW, Van Schil PE, Legrand C, Smit EF, Schramel F, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small cell lung cancer. *J Natl Cancer Inst*. 2007;99:442-50.
- Perrot E, Guibert B, Mulsant P, Blandin S, Arnaud I, Roy P, et al. Preoperative chemotherapy does not increase complications after non-small cell lung cancer resection. *Ann Thorac Surg*. 2005;80:423-7.
- Daly BD, Fernando HC, Ketchadjan A, Dipetrillo TA, Kachnic LA, Morelli DM, et al. Pneumonectomy after high-dose radiation and concurrent chemotherapy for non-small cell lung cancer. *Ann Thorac Surg*. 2006;82:227-31.
- Alexiou C, Beggs D, Rogers ML, Beggs L, Asopa S, Salama FD. Pneumonectomy for non-small cell lung cancer: predictors of mortality and survival. *Eur J Cardiothorac Surg*. 2001;20:476-80.
- Albain KS, Swann RS, Rusch VR, Turrisi AT, Shepherd FA, Smith CJ, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomized controlled trial. *Lancet*. 2009;374:379-86.
- Licker M, Spiliopoulos A, Frey JG, Robert J, Höhn L, de Perrot M, et al. Risk factor for early mortality and major complications following pneumonectomy for non-small cell lung carcinoma of the lung. *Chest*. 2002;121:1890-7.
- Van Raemdonck DE, Schneider A, Ginsberg RJ. Surgical treatment for higher stage non-small cell lung cancer. *Ann Thorac Surg*. 1992;54:999-1013.
- Stamatis G. Risks of neoadjuvant chemotherapy and radiation therapy. *Thorac Surg Clin*. 2008;18:71-80.
- Mansour Z, Kochetkova EA, Ducrocq X, Vasilescu MD, Maxant G, Buggenhout A, et al. Induction chemotherapy does not increase the operative risk of pneumonectomy. *Eur J Cardiothorac Surg*. 2007;32:181-5.
- Eberhardt W, Wilke H, Stamatis G, Stuschke M, Harstrik A, Menker H, et al. Preoperative chemotherapy followed by concurrent chemoradiation therapy based on hyperfractionated accelerated radiotherapy and definitive surgery in locally advanced non-small-cell lung cancer: mature results of a phase II trial. *J Clin Oncol*. 1998;16:622-34.
- Stamatis G, Eberhardt W, Pöttgen C. Surgery after multimodality treatment for non-small cell lung cancer. *Lung Cancer*. 2004;45(Suppl 2):107-12.

21. Van Schil P, Van Meerbeeck J, Kramer G, Splinter T, Legrand C, Giaccone G, et al. Morbidity and mortality in the surgery arm of EORTC 08941 trial. *Eur Respir J*. 2005;26:192-7.
22. DeCamp MM, Rice TW, Adelstein DJ, Chidel MA, Rybicki LA, Murthy SC, et al. Value of accelerated multimodality therapy in stage IIIA and IIIB non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2003;126:17-27.
23. Doddoli C, Thomas P, Thirion X, Serée Y, Giudicelli R, Fuentes P. Postoperative complications in relation with induction therapy for lung cancer. *Eur J Cardiothorac Surg*. 2001;20:385-90.
24. Stamatis G, Djuric D, Eberhardt W, Pöttken C, Zaboura G, Fechner S, et al. Post-operative morbidity and mortality after induction chemoradiotherapy for locally advanced lung cancer: an analysis of 350 operated patients. *Eur J Cardiothorac Surg*. 2002;22:292-7.
25. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *N Engl J Med*. 2003;27(349):2117-27.

Discussion

Dr Robert Cerfolio (Birmingham, Ala). These survival results are going to be unbelievable to many, especially when you have 27 patients with N3 disease and many with T4 disease. Therefore, can you tell us how you have such great survival in patients with N3, how you reassess N3, and are these nodes that are contiguous N3 as opposed to distant N3? As we all know, a Pancoast gives an N3 with a supraclavicular node, but that is really probably an N1. What kind of N3 nodes are these?

Dr Weder. Thank you for asking this question because this explains why we included N3 disease. As you know, the TNM staging system has its limitations, and N3 disease is not always N3 disease, N2 disease is not N2 disease. As you pointed out, in a centrally located tumor and a positive node adjacent to the tumor it is N2 or N3. By its biological behavior, it is probably most likely an N1 disease. You mentioned the Pancoast situation, where the supraclavicular lymph nodes are also not considered N3 but N1 disease.

Then there is another group of N3 disease that we have included, and this started when we had PET/CT scan available. We found isolated lymph nodes in the contralateral site at 1 station, and we asked ourselves the question, why do we have to exclude them? If they would be 5 mm closer to the ipsilateral site, it would be an N2 and we would do induction therapy. So we performed induction therapy followed by surgery in a couple of these patients, and we found long-term survival and even cure, and thereafter we did a phase II multicenter study including these patients, and this paper is currently under review for publication.

Dr Cerfolio. You heard yesterday in our breakout session how the medical oncologists and radiation oncologists want us to use curative doses of chemoradiotherapy beforehand, and I personally agree with that and made that cognitive leap almost 10 years ago, in 2000, and we have written about how it is safe to do a thoracotomy and pulmonary resection after 66 or even 70 Gy. You use 45 Gy. Are you going to make that cognitive leap, and do you think you can do a pneumonectomy after 60 or 66 cGy? Don't you think this offers maximal medical therapy in case surgery is not offered and thus avoids gaps and delays in the delivered amount of radiation dose before surgery?

Dr Weder. The more radiotherapy you apply, the higher risk of mortality and morbidity. This is clearly documented in the literature.

We have to balance this. How much risk do we want to take? This is a question that should be addressed by a multicenter study. We should compare 45 with 60 cGy and then go thereafter for surgery, because if you achieve good downstaging with 45 cGy and have resectability, then it favors this approach, because you have definitely less morbidity and mortality. So I favor a multicenter randomized study.

Dr Cerfolio. It sounds like you are not willing to make that leap, but we will talk about it later. My third and final question is the reassessment of N2 nodes. Most of us would say if those N2 nodes are still positive, we certainly wouldn't do a pneumonectomy, maybe a lobectomy in a young patient, but not a pneumonectomy. So tell me how you reassess the mediastinum (repeat endobronchial ultrasound, repeat endobronchial ultrasound-guided fine-needle aspiration, repeat mediastinoscopy), and when do you not believe the results based on the PET's percentage change in the maximum standardized uptake value and then do a more invasive biopsy, such as video-assisted thoracic surgery in the opposite chest, where the lesions are located?

Dr Weder. The reassessment is sometimes easy and sometimes difficult. I think it is easy for us when there is a good response to the treatment. We usually do not reassess the mediastinum in patients with a good response. They go for surgery directly. Those who are progressive are not candidates. But then there are the ones in between, and in our study they were reassessed by mediastinoscopy if this influenced the decision for resection, because at that time EBUS was not available yet, only maybe the last 1 or 2 years of the study.

Dr Mark Krasna (Towson, Md). Again, I'd like to focus on the group that received chemotherapy with radiation therapy, and I think that subgroup is of greatest interest to us. Tom Treasure's recent article in the *European Journal* emphasized that we don't always have to do a prospective randomized trial to answer an intuitively correct question. Your institution now is the sixth series in the thoracic literature, which is large enough for us to analyze results of pneumonectomy after chemoradiotherapy, and these results, like the ones from Rush, Alabama, our own in Baltimore, Ben Daley's group in Boston, and one from Poland last year, all show that you can do this treatment approach with less than 26% mortality and no difference between right and left.

My question to you is very specific regarding a patient who has N2 disease. If you were to give that patient chemotherapy and radiation therapy up front, as you see that your results of pathologic complete response are better than the rest, why are you persisting in only giving patients chemotherapy followed by surgery? Why not at least give all the patients chemotherapy with radiation at 45 cGy or, as Cerf says, chemotherapy with full-dose radiation at 60 cGy?

Dr Weder. I think scientifically the answer is not clear yet, and we are currently performing a study randomizing them in chemotherapy versus chemoradiotherapy.

Dr Krasna. There are no data in the literature to show a pathologic response rate anything greater than 4% with chemotherapy alone.

Dr Weder. Complete pathologic response is seen in 8% to 13% after chemotherapy alone. However, we used chemoradiotherapy in 80% of the patients, which may explain the higher response rate.