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)

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 surgical 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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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 irregularly 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).

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

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