Contemporary Results of Surgical Resection of Non-small Cell Lung Cancer After Induction Therapy

A Review of 549 Consecutive Cases

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Objective: We previously reported a high mortality after induction therapy and pneumonectomy for non-small cell lung cancer. Recent reports suggest that operative mortality in these patients is declining. We analyzed our contemporary results to define operative mortality and factors determining surgical risk.

Methods: Eligible patients were identified from our prospective surgical database. Complications were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events 3.0. Uni- and multivariate logistic regression models assessed the association of preoperative tests and clinical characteristics with outcome. Receiver operating characteristic curves and area under the receiver operating characteristic curve (AUC) statistics were calculated in a leave-one-out crossvalidation scheme to evaluate the predictive value of various models.

Results: From January 2000 to December 2006, 549 patients underwent surgery after induction therapy. Median patient age was 64 years (range: 30–86), and 54% were women (298/549). All received chemotherapy, and 17% also had radiation. Lobectomy (388/549, 71%) and pneumonectomy (70/549, 13%) were the most common procedures. Complications occurred in 250 patients (46%), with grade 3 or higher in 23% (126/549). Inhospital mortality was 1.8% (10/549), with only one death after right pneumonectomy (1/30, 3%). Multivariate analysis showed that predicted postoperative (PPO) pulmonary function was associated with postoperative morbidity. By receiver operating characteristic curves, PPO product (AUC = 0.75, $p < 0.001$), PPO diffusion capacity (AUC = 0.70, $p < 0.001$), and preoperative % predicted PPO diffusion capacity (AUC = 0.66, $p < 0.001$) predicted mortality.

Conclusion: Our current experience shows that resection of non-small cell lung cancer after induction therapy, including pneumonectomy, is associated with low mortality. PPO pulmonary function is the strongest predictor of operative risk and should be used to select patients for surgery.

Key Words: Lung cancer, Neoadjuvant therapy, Induction therapy, Surgical morbidity and mortality.

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Despite recent advances in the treatment of non-small cell lung cancer (NSCLC), long-term survival, even in early stage disease, is poor.[1,2] Nevertheless, in locally advanced disease, the addition of chemotherapy to surgical resection has been shown to improve survival rates relative to surgery alone.[3–10] Although induction chemotherapy is well tolerated,[9,10] prior studies, including a large one from our institution, reported high rates of postoperative morbidity and mortality in patients with NSCLC who received induction treatment.[11–13] We previously found that operative risk was especially high after right pneumonectomy, which was associated with a mortality of 23.9%. More recent series report declining morbidity and mortality.[14] In this study, we review our contemporary experience to define the frequency and types of postoperative adverse events after induction therapy and to identify factors that predict these events.

METHODS

Acquisition of Clinical Data

After approval by the institutional review board, we reviewed our prospectively maintained lung cancer database to identify patients who underwent surgery for NSCLC after induction therapy. Patients with superior sulcus and bilateral synchronous tumors were excluded because these were considered subgroups with factors that might confound analyses. Additional review of the medical record was done as needed

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to confirm patient demographics, preoperative treatment data, and perioperative measures.

Pulmonary comorbidity was defined as any underlying lung disease (most frequently chronic obstructive pulmonary disease). Postoperative % predicted DLCO (PPODLCO) and forced expiratory volume in 1 second (FEV1; PPOFEV1) were calculated either by segmental method (preoperative value multiplied by the number of bronchopulmonary segments remaining postoperatively and divided by 18) or by perfusion method (preoperative value multiplied by percentage perfusion in the remaining lung) in cases where quantitative ventilation perfusion scan was performed. PPODLCO and PPOFEV1 were then multiplied by one another to derive the predicted postoperative product (PPOP).[15]

Postoperative mortality was defined as death within 30 days of surgery or as death during the initial hospital stay if the patient was not discharged within 30 days. Complications were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (CTCAE 3.0) (http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf). Clinical and pathological tumor stages were assigned according to the 6th edition of the International System for Staging Lung Cancer.[16] Both CTCAE 3.0 and the 6th edition of the staging system were in force when this study was initiated. The extent of resection was classified as R0 (pathologically complete), R1 (residual microscopic disease), and R2 (residual macroscopic disease).

Statistical Methods

The association of PPO pulmonary function and clinical characteristics with perioperative outcomes was assessed by uni- and multivariate logistic regression. Known risk factors such as age, gender, smoking history, comorbidities, and surgical procedure were adjusted in the multivariate model. Based on the univariate empirical receiver operating characteristic (ROC) curve, the cutoff point for each measurement was chosen by the Youden index.[17] The ROC curves and the area under the ROC curve (AUC) were generated within a leave-one-out crossvalidation scheme. The estimated risks of mortality by three measurements were presented in smoothed curves using a secondary regression. All statistical analyses were performed in SAS 9.2 software (SAS Institute Inc., Cary, NC).

RESULTS

From January 2000 to December 2006, 629 consecutive patients underwent surgical exploration after induction therapy. Eighty patients were excluded (69 superior sulcus tumors and 11 cases of synchronous bilateral disease) leaving 549 for analysis. Patient characteristics are listed in Table 1. Median patient age was 64 years (range: 30–86 years), and 54% (298/549) were women. Most patients (90%) were current or former smokers. The majority of patients undergoing preoperative therapy had clinical stage II to stage IIIA tumors (389/549, 71%). A small number of patients ($n = 15$) with clinical stage IA disease were treated with preoperative chemotherapy for various reasons (e.g., small cell lung cancer harboring persistent NSCLC after definitive nonsurgical therapy). Mean % predicted FEV1 was 85% ± 18% (range: 27–141), and the mean % predicted DLCO was 73% ± 20% (range: 12–135).

TABLE 1. Patient Characteristics

Characteristics	Patients ($n = 549$)
Age, yr (range)	64 (30–86)
Gender (female)	298 (54%)
Smoking status	
Never	56 (10.2%)
Former	424 (77%)
Current	69 (13%)
Mean pack years (SD)	43 (±32)
Comorbidities	
Pulmonary	133 (24%)
Cardiac	222 (40%)
Renal	7 (1%)
Endocrine	40 (7%)
Other	127 (23%)
Pretreatment clinical stage	
IA	15 (3%)
IB	68 (12%)
IIA	8 (1%)
IIB	83 (15%)
IIIA	305 (56%)
IIIB	49 (9%)
IV	21 (4%)
Pulmonary function mean (SD)	
FEV1 % predicted	85 (18)
DLCO % predicted	73 (20)
PPOFEV1 segmental	66 (18)
PPODLCO segmental	57 (19)
PPOP segmental	40 (21)
PPOFEV1 perfusion	63 (16)[a]
PPODLCO perfusion	55 (16)[a]

[a] Quantitative perfusion scans were undertaken in 193/549 patients (35%).

PPO, predicted postoperative; FEV1, forced expiratory volume in 1 second; DLCO, PPO diffusion capacity; PPOP, predicted postoperative product.

Preoperative chemotherapy, usually cisplatin based, was administered to 545 patients (99%), and 95 (17%) of patients also had external beam radiotherapy. The median radiation dose was 50 Gy (range: 15–70 Gy) and was administered concurrently to 80 of 95 (92%) and sequentially to 7 of 95 (8%) patients. Details of timing of administration in the remaining eight patients were not available.

The details of surgery are listed in Table 2. Lobectomy was the most common procedure. Pneumonectomy was performed in 13% (70/549) of patients and was right sided in 30 of 70 patients (44%). Concomitant en bloc chest wall resection was performed in 30 patients. Complete macroscopic resection (R0 and R1) was achieved in 89% (489/549) of patients with RO resection in 83.4% (458/549) patients.

Perioperative Adverse Events

The median length of hospital stay was 6 days (range: 1–108). The total operative morbidity rate for the group was

