Long-Term Outcomes of Lobectomy for Non-Small Cell Lung Cancer After Definitive Radiation Treatment

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Background. **Salvage surgical resection for non-small cell lung cancer (NSCLC) patients initially treated with definitive chemotherapy and radiotherapy can be performed safely, but the long-term benefits are not well characterized.**

Methods. **Perioperative complications and long-term survival of all patients with NSCLC who received curative-intent definitive radiotherapy, with or without chemotherapy, followed by lobectomy from 1995 to 2012 were evaluated.**

Results. **During the study period, 31 patients met the inclusion criteria. Clinical stage distribution was stage I in 2 (6%), stage II in 5 (16%), stage IIIA in 15 (48%), stage IIIB in 5 (16%), stage IV in 3 (10%), and unknown in 1 (3%). The reasons surgical resection was initially not considered were: patients deemed medically inoperable (5 [16%]); extent of disease was considered unresectable (21 [68%]); small cell lung cancer misdiagnosis (1 [3%]), and unknown (4 [13%]). Definitive therapy was irradiation alone in 2 (6%), concurrent chemoradiotherapy in 28 (90%), and sequential chemoradiotherapy in 1 (3%). The median radiation dose was 60 Gy. Patients were subsequently referred for resection because of obvious local relapse, medical tolerance of surgical intervention, or posttherapy imaging suggesting residual disease. The median time from radiation to lobectomy was 17.7 weeks. There were no perioperative deaths, and morbidity occurred in 15 patients (48%). None of the 3 patients with residual pathologic nodal disease survived longer than 37 months, but the 5-year survival of pN0 patients was 36%. Patients who underwent lobectomy for obvious relapse (n = 3) also did poorly, with a median overall survival of 9 months.**

Conclusions. **Lobectomy after definitive radiotherapy can be done safely and is associated with reasonable long-term survival, particularly when patients do not have residual nodal disease.**

(Ann Thorac Surg 2015;99:1914–20)

Definitive irradiation is indicated for patients with inoperable non-small cell lung cancer (NSCLC) [1], but approximately 30% of patients with locally advanced NSCLC experience local-regional recurrence after curative-intent chemotherapy and radiotherapy [2]. Salvage primary tumor resection is sometimes considered for isolated local failures after definitive chemoradiation [3, 4] but is generally considered technically more difficult, with potentially higher morbidity than when resection is performed after planned induction therapy. This increased complexity of salvage surgical resection is felt to result from higher radiation doses as well as from the typically longer periods between radiotherapy and surgical resection. Salvage lung resection is often not considered until more than 12 weeks after radiotherapy [3], whereas surgical resection is usually performed 3 to 8 weeks after planned induction radiotherapy [3, 5]. This increased time typically leads to operating in a field of radiation fibrosis with obliterated planes and tissue hypovascularity that makes dissection more difficult and also may impair wound healing [3].

Several studies have shown that lung resections can be safely performed after high-dose radiotherapy [3, 6–14]. However, these studies have generally been small and the operations were not considered salvage resections, and the potential long-term survival benefits of surgical resection in this situation have not been well characterized. This study was undertaken to examine long-term outcomes of lobectomy for NSCLC after definitive radiotherapy and provide quantitative data regarding the

Accepted for publication Jan 16, 2015.

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Dr D'Amico discloses a financial relationship with Scanlan International, Inc.

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2015.01.064

benefits of surgical resection that can assist surgeons in the treatment decision process when they are evaluating patients in this clinical scenario.

Material and Methods

After obtaining Institutional Review Board approval with waiver of individual patient consent, a retrospective analysis of all NSCLC patients who received curative-intent definitive radiotherapy, with or without chemotherapy, followed by lobectomy at Duke University Medical Center between January 1995 and November 2012 was performed. Administration of definitive chemoradiation vs definitive radiotherapy alone was determined by the therapy protocols and physician preference, administered at several institutions, and therefore, was not standardized. Patient inclusion criteria were (1) biopsy-proven NSCLC before any therapy, (2) prior curative-intent radiotherapy with or without chemotherapy, (3) no a priori plan for eventual surgical resection, and (4) subsequent salvage lobectomy. A thoracic surgeon, medical oncologist, and radiation oncologist evaluated each patient before salvage resection. Lung cancers were staged according to the American Joint Committee on Cancer (AJCC) Seventh Edition of Lung Cancer Staging guidelines; patients treated at the time of earlier staging systems were recoded according to Seventh Edition definitions [15].

Baseline variables collected included demographics, comorbidities, tobacco use, pulmonary function, histologic evaluation, pretreatment clinical stage, and radiotherapy and chemotherapy regimens. The use of noninvasive (positron emission tomography [PET] and computed tomography [CT]) and invasive (cervical mediastinoscopy or endobronchial ultrasound) staging studies before initial therapy and ultimate resection was also examined. Mediastinal lymph node dissection at the time of resection was routinely performed as previously described [16]. Perioperative variables collected included pathologic stage and operative and postoperative course, including details on chest tube duration, hospital length of stay, and complications. Outcome variables collected were overall and recurrence-free survival.

Overall survival and recurrence-free survival analyses were performed according to the Kaplan-Meier method and included all deaths from any cause in the follow-up period, with patients still alive censored at the last available follow-up. Overall survival was calculated from the time of lobectomy to death from any cause, with patients censored at the time of the last follow-up at Duke University Medical Center. Recurrence-free survival was calculated from the time of lobectomy to recurrence seen on imaging or death, again with patients censored at the time of the last follow-up. A multivariable Cox proportional hazard model for survival that included age, sex, pretreatment clinical stage, and residual disease as covariates was also fitted.

Patients were also grouped by primary indication for salvage lung resection in a similar fashion as previously described [3]:

1. Obvious local relapse—patients whose PET scans after definitive radiotherapy initially showed no 2-dexoy-2-18F-fluoro-D-glucose (FDG) uptake but subsequently demonstrated increased FDG uptake at the site of primary tumor, diagnosed as relapse, with biopsy done in most patients.
2. Medical tolerance of surgical resection—patients previously deemed inoperable due to insufficient respiratory reserve or general frailty but who were considered appropriate surgical candidates after reevaluation with another provider or after having undergone sufficient rehabilitation and improvement.
3. Radiologic imaging that suggested residual disease—patients with CT imaging suggesting residual disease or PET demonstrating hypermetabolic abnormality within the primary tumor or locoregional lymph nodes.

In this scenario, surgeons often accepted the CT or FDG-PET results as a surrogate of risk for residual disease without preoperative tissue confirmation due to the known poor sensitivity and negative-predictive value of percutaneous biopsy specimens after definitive chemoradiation [3]. Survival of subgroups was compared using the log-rank test. Statistical analyses were performed using Stata 12.0 software (StataCorp LP, College Station, TX).

Results

Preresection Evaluation and Management

During the study period, 31 patients met the inclusion criteria (Table 1). The median age at the time of resection was 58 years (range, 40 to 78 years), and 13 patients (42%) were female. Chronic obstructive pulmonary disease (COPD) was the most common comorbidity, and 23% of patients had previously undergone thoracic operations. Clinical staging data before any treatment are also detailed in Table 1. All patients underwent a baseline chest CT and FDG-PET scan and full pulmonary function tests as part of their initial staging evaluation, and 17 (55%) underwent CT or magnetic resonance image (MRI), or both, of the brain. Only 10 patients (32%) underwent invasive mediastinal staging before receiving definitive radiotherapy. Seven of 15 patients who were clinically staged as having N2 disease had pathologic confirmation before starting treatment. No patients underwent resection for staging purposes.

In 26 of 31 patients, the initial staging and decisions for definitive radiation treatment were made at an outside institution, and the patients were subsequently referred to a tertiary care center to consider salvage lung resection after completing definitive radiotherapy. A surgeon participated in 11 of 31 initial staging and treatment evaluations (35%). All surgeons who performed the reevaluation after definitive radiotherapy performed the operation. The reasons definitive radiotherapy were pursued instead of surgical resection are detailed in Table 2. Of the 5 patients deemed medically inoperable, this decision was made in 4 patients without a formal evaluation by a surgeon.