Stereotactic body radiation therapy versus surgical resection for stage I non–small cell lung cancer

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Objectives: Stereotactic body radiation therapy has been proposed as an alternative local treatment option for high-risk patients with early-stage lung cancer. A direct comparison of outcomes between stereotactic body radiation therapy and surgical resection has not been reported. This study compares short-term outcomes between stereotactic body radiation therapy and surgical treatment of non–small cell lung cancer.

Methods: We compared all patients treated with surgery (January 2000–December 2006) or stereotactic body radiation therapy (February 2004–May 2007) with clinical stage IA/B non–small cell lung cancer staged by computed tomography and positron emission tomography. Comorbidity scores were recorded prospectively using the Adult Co-Morbidity Evaluation scoring system. Charts were reviewed to determine local tumor recurrence, disease-specific survival, and overall survival. A propensity score matching analysis was used to adjust estimated treatment hazard ratios for confounding effects of patient age, comorbidity index, and clinical stage.

Results: A total of 462 patients underwent surgery and 76 received stereotactic body radiation therapy. Overall, surgical patients were younger ($P < .001$), had lower comorbidity scores ($P < .001$), and better pulmonary function (forced expiratory volume in 1 second and carbon monoxide diffusion in the lung) ($P < .001$). Among the surgical and stereotactic body radiation therapy groups, 62.6% (291/462) and 78.9% (60/76) were in clinical stage IA, respectively. Final pathology upstaged 35% (161/462) of the surgery patients. In an unmatched comparison, overall 5-year survival was 55% with surgery, and the 3-year survival was 32% with radiation therapy. Among patients with clinical stage IA disease, 3-year local tumor control was 89% with radiation therapy and 96% with surgery ($P = .04$). There was no difference in local tumor control in stage IB disease ($P = .89$). No disease-specific survival differences were found in patients with 1A ($P = .33$) or IB disease ($P = .69$). Propensity analysis matched 57 high-risk surgical patients to 57 patients undergoing stereotactic body radiation therapy. In the matched comparison of this subgroup, there was no difference in freedom from local recurrence (88% vs 90%), disease-free survival (77% vs 86%), and overall survival (54% vs 38%) at 3 years.

Conclusions: In an unmatched comparison of clinical stage IA disease, surgical patients were healthier and had better local tumor control compared with those receiving stereotactic body radiation therapy. Propensity analysis in clinical stage IA/B non–small cell lung cancer revealed similar rates of local recurrence and disease-specific survival in patients treated with surgery compared with stereotactic body radiation therapy. (J Thorac Cardiovasc Surg 2010;140:377-86)

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Optimal management of very high-risk patients with early-stage lung cancer remains a difficult challenge for the treating physician. Poor pulmonary function and cardiac-related morbidity can limit the available treatment options. Although it is speculated that mortality in these high-risk patients commonly results from their comorbid conditions, population-based studies have shown that when left untreated, patients with early-stage lung cancer die of their cancer, rather than of competing causes of death.[1,2]

Although surgical resection remains the standard of care for early-stage lung cancer, new technology in radiation therapy provides for more concentrated, focused therapy that may improve efficacy and decrease toxicity compared with traditional external beam radiation. Stereotactic radiation therapy has been used for many years for the treatment of intracranial lesions not amenable to surgical resection. The application of this therapy has been extended to extracranial tumors and is often referred to as stereotactic body radiation therapy (SBRT). SBRT delivers high-dose radiation over 3 to 5 treatment fractions using multiple conformal coplanar and non-coplanar beams. This technique concentrates the prescribed radiation dose to the tumor more

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Abbreviations and Acronyms

ACE-27 = Adult Co-Morbidity Evaluation-27
CT = computed tomograph
FEV_1 = forced expiratory volume in 1 second
NSCLC = non–small cell lung cancer
PET = positron emission tomography
PSM = propensity score matching
SBRT = stereotactic body radiation therapy

precisely than conventional radiation therapy. Local tumor control rates with SBRT range between 85% and 95% at 3 to 5 years.[3-7] SBRT also limits the acute complications frequently seen with external beam therapy.[3-6] Severe acute toxicity from SBRT ranges from 2% to 8% with only 1 reported treatment-related death in several studies.[5-7]

Many prospective studies of SBRT in high-risk patients have been reported, with 2-year survival ranging from 47% to 77%.[3,4,7,8] Five-year survival has been reported as 36.5% to 47% with longer follow-up.[3-7] Examining the surgical experience in patients of varying risks, 5-year survival for pathologic stage IA and IB disease is 73% and 54%, respectively.[9] For clinical stage IA and IB disease, the 5-year survival is 50% and 40%, respectively.[9] Although prospective clinical trials are underway, there are no direct comparisons of SBRT versus surgery in the management of early-stage lung cancer to date.

Our primary objective is to compare short-term outcomes between patients undergoing primary treatment with SBRT versus surgical resection for clinical stage I non–small cell lung cancer (NSCLC) (T1 or T2 N0 M0) at our institution. Propensity matched analysis enabled comparisons between high-risk patients in the surgical group and patients receiving SBRT to examine survival in this subgroup.

METHODS

All surgical patients with clinical stage I lung cancer treated between January 1, 2000, and December 31, 2006, and all patients between February 1, 2004, and May 5, 2007, with clinical stage I lung cancer undergoing treatment with SBRT were included and analyzed according to a protocol approved by our institutional review board. Not all patients receiving SBRT in this study had pathologic diagnoses, although referral for a computed tomography (CT)-guided biopsy was requested in all patients. The patients without a histologic diagnosis were considered to be too high of a risk for pneumothorax by our inteventional radiologists. A biopsy was refused by 3 patients. In addition, all tumors in the SBRT group were nodular lesions that were very suggestive of malignancy (ie, solid, spiculated) by CT or demonstrated growth on serial CT scans. Each of these patients underwent positron emission tomography–computed tomography (PET-CT) for staging. None had evidence of metastatic adenopathy and each of the lesions subjected to SBRT was considered malignant. The very high-risk patients undergoing SBRT did not routinely undergo staging mediastinoscopy or endobronchial ultrasonography. Clinical staging was done with CT and PET imaging in these patients. All CT scans and PET scans were reviewed in the surgical group to include only those patients with clinical stage I lung cancer. Comorbidity scores were recorded prospectively using the Adult Co-Morbidity Evaluation (ACE-27) scoring system. Charts were reviewed to determine local tumor recurrence, disease-specific survival, and overall survival. Propensity score matching (PSM) was performed on the basis of preoperative comorbidities and lung function. The ACE-27 form (Appendix A) was used to stratify pretreatment comorbidity in both groups. The comorbidity scores on all patients included in the trial were collected prospectively from the Oncology Data Services database managed by the Clinical Outcomes Research Office at Washington University. Exclusion criteria include patients with small cell lung cancer or other cancers that had metastasized to the lung, patients undergoing resection for benign disease, patients without preoperative staging chest CT and fluorodeoxyglucose PET scans, patients with tumors graded T3 or greater, patients with clinical N1 or N2 disease noted on preoperative imaging, and patients with concurrent malignancy within the year before treatment. Data on patient demographics, history and physical examination, evaluation by chest CT, fluorodeoxyglucose PET scans, operative report, and final pathology reports (where available) were obtained from medical records.

In the surgical patients, the type of incision, type of resection (ie, lobar or sublobar), and extent of lymph node dissection were at the discretion of the treating surgeon. Patients undergoing SBRT were discussed at a multidisciplinary conference and were deemed to have inoperable disease by thoracic surgeons unless the patient simply refused surgical intervention. Current standard dosing delivers 54 Gy in 3 fractions over 8 to 14 days as currently recommended by the Radiation Therapy Oncology Group. The SBRT device used in this study is the Trilogy system produced by Varian Medical Systems, Inc (Palo Alto, Calif). This device does not generally require the placement of fiducial markers. Each tumor is localized by cone-beam CT on the Trilogy unit, axial, coronal, and sagittal alignment is matched to the treatment plan, and therapy is delivered. In a few of our patients, fiducial markers were placed to help clarify tumor position because of location near the mediastinum or diaphragm. A total of 10 to 12 non-coplanar beams deliver the prescribed radiation dose to the periphery of the planning target volume. The dose is typically prescribed to the 80% to 85% isodose line, meaning that the center of the tumor received a dose that is 15% to 20% higher than the prescription. Toxicity of SBRT was graded using the National Cancer Institutes Common Toxicity Criteria version 3.0.

Statistical analysis was performed using SPSS 11.0 for Windows (SPSS, Inc, Chicago, Ill) and Matlab (Mathworks, Inc, Natick, Mass). Descriptive statistics such as mean and median were presented for continuous variables whereas counts and proportions were presented for categorical data. Differences in mean were estimated by 2-tailed t test, in median using the Wilcoxon rank sum, and in proportions using the χ^2 test. Multivariate analysis of prognostic factors was performed using the Cox proportional hazards model. Treatment groups matching based on selected covariates was performed using PSM. In the PSM analysis, logistic regression was used to estimate the corresponding scores from the baseline patient covariates. To find matched patients from the 2 groups, we adopted a caliper matching approach. In this approach, both treatment groups are randomly sorted and then the datasets are matched using nearest neighbor distance in terms of the propensity score that is within an acceptable distance, called a ''caliper.'' This approach has the ability to avoid bad matches (too large differences in propensity scores) compared with classic PSM methods.

RESULTS

A total of 462 patients with clinical stage I disease met inclusion criteria and underwent surgical resection during the defined study period whereas 76 underwent SBRT since the institution of this technology. All patients among each treatment group were clinically staged with CT and PET imaging. Median follow-up in the SBRT and surgical groups was 19 and 31 months, respectively.