Analysis of first recurrence and survival in patients with stage I non–small cell lung cancer treated with surgical resection or stereotactic radiation therapy

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Objectives: Comparative studies of survival between stereotactic body radiation therapy (SBRT) and surgery have been limited by lack of comparisons of recurrence patterns between matched cohorts in non−small cell lung cancer (NSCLC).

Methods: All patients undergoing treatment with surgery or SBRT for clinical stage I NSCLC between June 2004 and December 2010 were reviewed. Age, tumor characteristics, comorbidity score, pulmonary function, overall survival (OS), disease-free survival (DFS), and recurrence data were collected and propensity matching performed.

Results: The mean age for surgery (n = 458) was 65.8 ± 10.5 versus 74.4 ± 9.4 for SBRT (n = 151) ($P < .0001$). For the entire surgical cohort, 3-year OS was 78% and DFS was 72%. For the entire SBRT cohort, 3-year OS was 47% and DFS was 42%. The overall local recurrence rate for surgery was 2.6%. The overall local recurrence rate for SBRT was 10.7%. A propensity-matched comparison based on age, tumor size, Adult Comorbidity Evaluation comorbidity score, forced expiratory volume in the first second of expiration, and tumor location resulted in 56 matched pairs. The 3-year OS was 52% versus 68% for SBRT and surgery ($P = .05$); DFS was 47% versus 65% ($P = .01$). At 3 years, local recurrence-free survival was 90% versus 92% for SBRT and surgery ($P = .07$).

Conclusions: Although surgical resection seems to result in better OS and DFS versus SBRT, matching these disparate cohorts of patients remains challenging. Participation in clinical trials is essential to define the indications and relative efficacy of surgery and radiation therapy in a high-risk population with stage I NSCLC. (J Thorac Cardiovasc Surg 2014;147:1183-92)

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Stereotactic body radiation therapy (SBRT) has become the primary treatment of choice for inoperable patients with peripheral stage I lung cancer. Although the role of radiofrequency ablation has yet to be defined for stage I lung cancer, single-center studies and a prospective trial of SBRT have consistently demonstrated good cancer-specific survival in patients deemed inoperable.[1-4] For SBRT, 3-year survival for stage I lung cancer has been reported to be 56% to 85% with primary tumor local recurrence rates less than 10% at 3 years.[2-7] These data have highlighted the benefit of this therapy in a cohort of patients who previously went untreated or were inadequately treated with conventional external beam radiation therapy.

Currently, surgical anatomic resection with mediastinal lymphadenectomy remains the standard of care for operable patients with stage I lung cancer.[8,9] In the contemporary era of video-assisted techniques for anatomic resection, 5-year overall survival (OS) has been reported to be 75% to 80% with a perioperative mortality rate of 1%.[10-12] In small subsets of potentially operable patients from single-center studies, SBRT has been associated with good primary tumor control and OS. Although such findings are encouraging, these data are not sufficient to supplant surgical resection

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Abbreviations and Acronyms

ACE-27 = Adult Comorbidity Evaluation-27
ACOSOG = American College of Surgeons Oncology Group
BED = biologically effective dose
CT = computed tomography
DFS = disease-free survival
FDG = 2-deoxy-2[^{18}F]fluoro-D-glucose
FEV_1 = forced expiratory volume in the first second of expiration
HIV = human immunodeficiency virus
NSCLC = non−small cell lung cancer
OS = overall survival
PET = positron emission tomography
RTOG = Radiation Therapy Oncology Group
SBRT = stereotactic body radiation therapy

as the standard of care in the operable patient and clinical trials are needed to determine whether outcomes after SBRT are comparable with anatomic surgical resection.[2,3,13]

The ambiguous scenario, however, involves the so-called high-risk surgical patient with early stage lung cancer. The American College of Surgeons Oncology Group (ACOSOG) Z4032 trial has recently examined the role of sublobar resection with and without brachytherapy in this subgroup of patients.[14] The ACOSOG Z4099/Radiation Therapy Oncology Group (RTOG) 1021 trial was an important prospective randomized trial designed to compare outcomes in high-risk patients with stage I lung cancer treated with sublobar resection versus SBRT.[15] Unfortunately, because of poor accrual, this trial was recently closed. Our institution has published previous comparative studies demonstrating comparable cancer-specific survival after surgery in propensity-matched groups of patients treated with either SBRT or surgery.[16-18] Limitations of previously published series include small sample size, inadequate follow-up, inconsistent definitions of recurrence between the groups, and inadequate matching of the cohorts.

This study was designed to overcome some of the shortcomings of previously published comparisons. This is a retrospective propensity-matched comparative study using a large cohort of patients undergoing SBRT or surgical resection for stage I lung cancer. This study was designed to compare OS, disease-free survival (DFS), local recurrence, regional recurrence, and distant recurrence using common definitions of recurrence and survival from recent and ongoing clinical trials.

METHODS

This is a retrospective study of all patients undergoing treatment at our center with surgery or SBRT for clinical stage I non–small cell lung cancer (NSCLC) between June 2004 and December 2010. The patients were treated at the Siteman Cancer Center, a National Cancer Institute–designated comprehensive cancer center at the Washington University School of Medicine and Barnes-Jewish Hospital in Saint Louis, Missouri. All patients underwent clinical staging with computed tomography (CT) and fluorodeoxyglucose (FDG)-positron emission tomography (PET) imaging. Patients were usually seen initially by a surgeon, and if considered high-risk for lobectomy were referred for SBRT. In the surgical patients, the type of surgical resection performed (ie, lobar vs sublobar), the type of incision, performance of mediastinoscopy, and extent of lymph node dissection was at the discretion of the treating thoracic surgeon. NSCLC was ultimately confirmed histologically in all surgical patients. Patients undergoing SBRT did not undergo routine surgical staging with either mediastinoscopy or endobronchial ultrasonography.

All pretreatment CT scans and FDG-PET scans were reviewed to include only those patients with clinical stage I lung cancer. Comorbidity scores were recorded prospectively using the Adult Comorbidity Evaluation (ACE-27) scoring system (Appendix E1). The Siteman Cancer Center Oncology Data Services in the Clinical Outcomes Research Office at Washington University prospectively assigns comorbidity scores.

Clinic and hospital charts, follow-up CT and FDG-PET scans, as well as follow-up biopsies were reviewed to determine local tumor recurrence, regional and distant recurrence, DFS, and OS. Patients were followed with serial chest radiographs and/or CT scans every 3 to 6 months for the first 2 years and every 6 to 12 months up to 5 years, then yearly afterward. FDG-PET imaging was performed if there was suspicion for recurrence. Local, regional, and distant recurrence definitions were as defined by the current ACOSOG Z4099/RTOG 1021 trial for comparison of SBRT and sublobar resection in high-risk patients.[19] Briefly, local recurrence included the primary tumor site, marginal, ipsilateral lobar, or port site/wound recurrence. An important distinction in this trial is the definition of local recurrence, which includes both primary tumor failure and (for sublobar resection or SBRT) failure in the involved lobe. In some instances, the diagnosis of the first recurrence occurred simultaneously at different locations accounting for the multiple recurrences noted in some patients. Exclusion criteria included patients with small cell lung cancer or extrathoracic cancers that metastasized to the lung, patients undergoing resection for benign disease, patients without preoperative staging chest CT and FDG-PET scans, patients with tumors stages or T3 or higher and patients with clinical N1 or N2 disease noted on preoperative imaging. For the SBRT patients, every effort was made to obtain a tissue diagnosis before treatment. A small fraction (14%) of patients underwent treatment without a tissue diagnosis. These patients were reviewed at our multidisciplinary conference and in all such patients, a radiologist reviewed the images and either attempted a biopsy or deemed a biopsy to be too high risk. These patients were included to demonstrate the practical management of clinical stage I lung cancer in high-risk or inoperable patients and to provide a reference for the proportion of patients treated without a tissue diagnosis relative to other published cohorts.

Details of SBRT planning and delivery at our institution have been described previously.[1] The Varian Trilogy System was used for all SBRT patients. Target coverage, conformality, and normal tissue constraints were followed according to the protocol for the RTOG 0236 clinical trial.[7] Prescriptions were typically specified at the 60% to 90% (median, 84%) isodose line so that at least 95% of the prescribed dose covered the planning target volume. Most SBRT patients received a biologically effective dose (BED) of at least 100 Gy_{10} (median dose, 54 Gy in 3 fractions). BED was calculated using $BED_{\alpha/\beta} = nd\,(1 + d/\alpha/\beta)$, where n is the number of fractions, d is the dose per fraction, and $\alpha/\beta = 10$ for tumor in line with previous reports.[5,20]

BED_{10} for the SBRT regimens used in this study was 85.5 Gy_{10} (45 Gy in 5 fractions, n = 6), 86.4 Gy_{10} (48 Gy in 6 fractions, n = 1), 100 Gy_{10} (50 Gy in 5 fractions, n = 21), 105.6 Gy_{10} (48 Gy in 4 fractions, n = 1), 112.5 Gy_{10} (45 Gy in 3 fractions, n = 6), 115.5 Gy_{10} (55 Gy in 5 fractions, n = 3), 132 Gy_{10} (60 Gy in 5 fractions, n = 4), and 151.2 Gy_{10} (54 Gy in 3 fractions, n = 110).