Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer

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WHILE ANATOMICAL RESEC-tion is the standard treatment for early stage lung cancer, some patients cannot tolerate surgery due to comorbidities such as emphysema and heart disease. These patients are deemed medically inoperable and are generally offered conventional radiotherapy (most commonly given during 20-30 outpatient treatments) or observed without specific cancer therapy. Outcomes are not ideal with either approach. Conventional radiotherapy fails to durably control the primary lung tumor in 60% to 70% of patients.[1-3] More than half of patients ultimately die specifically from progressive lung cancer with observation[4,5] and 2-year survival is less than 40% with either approach.

Stereotactic body radiation therapy (SBRT) is a noninvasive cancer treatment in which numerous small, highly focused, and accurate radiation beams are used to deliver potent doses in 1 to 5 treatments to tumor targets in extra-cranial sites.[6] Consensus publications describing the conduct and technical requirements of SBRT have been published.[7] Numerous single institution studies have shown that SBRT is an effective and well-tolerated treatment for early stage lung cancer in medically inoperable patients.[8-10] The Radiation Therapy Oncology Group (RTOG) 0236 trial was the first North American multicenter, cooperative group study to test SBRT in treating medically inoperable patients with early stage

Context Patients with early stage but medically inoperable lung cancer have a poor rate of primary tumor control (30%-40%) and a high rate of mortality (3-year survival, 20%-35%) with current management.

Objective To evaluate the toxicity and efficacy of stereotactic body radiation therapy in a high-risk population of patients with early stage but medically inoperable lung cancer.

Design, Setting, and Patients Phase 2 North American multicenter study of patients aged 18 years or older with biopsy-proven peripheral T1-T2N0M0 non–small cell tumors (measuring <5 cm in diameter) and medical conditions precluding surgical treatment. The prescription dose was 18 Gy per fraction × 3 fractions (54 Gy total) with entire treatment lasting between 1½ and 2 weeks. The study opened May 26, 2004, and closed October 13, 2006; data were analyzed through August 31, 2009.

Main Outcome Measures The primary end point was 2-year actuarial primary tumor control; secondary end points were disease-free survival (ie, primary tumor, involved lobe, regional, and disseminated recurrence), treatment-related toxicity, and overall survival.

Results A total of 59 patients accrued, of which 55 were evaluable (44 patients with T1 tumors and 11 patients with T2 tumors) with a median follow-up of 34.4 months (range, 4.8-49.9 months). Only 1 patient had a primary tumor failure; the estimated 3-year primary tumor control rate was 97.6% (95% confidence interval [CI], 84.3%-99.7%). Three patients had recurrence within the involved lobe; the 3-year primary tumor and involved lobe (local) control rate was 90.6% (95% CI, 76.0%-96.5%). Two patients experienced regional failure; the local-regional control rate was 87.2% (95% CI, 71.0%-94.7%). Eleven patients experienced disseminated recurrence; the 3-year rate of disseminated failure was 22.1% (95% CI, 12.3%-37.8%). The rates for disease-free survival and overall survival at 3 years were 48.3% (95% CI, 34.4%-60.8%) and 55.8% (95% CI, 41.6%-67.9%), respectively. The median overall survival was 48.1 months (95% CI, 29.6 months to not reached). Protocol-specified treatment-related grade 3 adverse events were reported in 7 patients (12.7%; 95% CI, 9.6%-15.8%); grade 4 adverse events were reported in 2 patients (3.6%; 95% CI, 2.7%-4.5%). No grade 5 adverse events were reported.

Conclusion Patients with inoperable non–small cell lung cancer who received stereotactic body radiation therapy had a survival rate of 55.8% at 3 years, high rates of local tumor control, and moderate treatment-related morbidity.

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non–small cell lung cancer. In this article, the 3-year results from RTOG 0236 are described.

METHODS

Patient Eligibility

Patients had to be aged 18 years or older with a Zubrod performance status score of 0 (fully active, unrestricted), 1 (restricted activities but able to work), or 2 (cares for self but unable to work). Cytological or histological proof of non–small cell cancer was required for entry. Eligible patients could have American Joint Committee on Cancer stages T1-T2 ($\leq$5 cm) or T3 ($\leq$5 cm peripheral tumors only) N0M0 cancer based on both mandatory computed tomography (CT) and positron emission tomography (PET) screening. While a subset of patients with T3 tumors were eligible, ultimately none were enrolled making the study results not necessarily pertinent to the T3 subset. The treated tumor was required to be greater than 2 cm in all directions from the proximal bronchial tree, which was defined as the distal 2 cm of the trachea, carina, and named major lobar bronchi up to their first bifurcation. Patients were ineligible if they had a synchronous malignancy within 2 years of entry. Patients also were ineligible if they had a history of prior radiotherapy to the thorax; active systemic, pulmonary, or pericardial infection; or were pregnant or lactating. Patients with plans to receive conventional radiotherapy, chemotherapy, biological therapy, vaccine therapy, or surgery as treatment (except at disease progression) were ineligible. Operable patients were ineligible. Data regarding race and ethnicity were collected from the registering site as per reporting requirements of the study sponsor (the US National Cancer Institute); however, this information was not used in patient selection. All patients were required to sign informed consent prior to study registration.

Prior to enrollment, patients were required to be evaluated by an experienced thoracic surgeon or pulmonologist to determine operability. Standard indicators defining a patient to be medically inoperable included baseline forced expiratory volume in the first second of expiration (FEV_1) of less than 40% predicted, predicted postoperative FEV_1 of less than 30% predicted, carbon monoxide diffusing capacity of less than 40% predicted, baseline hypoxemia or hypercapnia, severe pulmonary hypertension; diabetes mellitus with end-organ damage; severe cerebral, cardiovascular, or peripheral vascular disease; or severe chronic heart disease.

Radiotherapy Specifications

The gross tumor volume was outlined on pulmonary CT windows, excluding soft tissue densities with standard uptake values of less than 2 on PET scans (likely to be atelectasis). No additional margin was added for possible microscopic extension. An institution-appropriate error margin beyond this gross tumor volume (defined as the planning target volume), which included both set-up error and error related to motion, was limited to no more than 5 mm in the axial dimension and 10 mm in the craniocaudal dimension.

Patients received 60 Gy in 3 fractions of 20 Gy per fraction, which was prescribed to the edge of the planning target volume. Each fraction was separated by at least 40 hours (at most, by 8 days). The entire 3 fraction regimen was required to be completed within 14 days. Only 4 to 10 mV photon beams were allowed. For planning, no tissue density heterogeneity correction was allowed. Later analysis, using proper accounting of density heterogeneity, showed that the RTOG 0236 trial overpredicted the actual planning target volume dose such that the delivered dose was actually closer to 54 Gy in 3 fractions of 18 Gy.[11]

Image guidance capable of confirming the position of the target with each treatment was required. Tumor motion related to respiration was required to be quantified using fluoroscopy or 4-dimensional CT scans. If the motion confirmed with free breathing was greater than the maximum planning target volume expansions allowed by the protocol, a method of motion control such as abdominal compression, gating, or breath holding was required.

Adequate target coverage was achieved when 95% of the planning target volume was covered by 60 Gy and when 99% of the planning target volume received at least 54 Gy. High-dose conformality was controlled such that the volume of tissue outside of the planning target volume receiving a dose greater than 63 Gy must be less than 15% of the planning target volume and the target conformality index (ratio of the volume receiving 60 Gy to the planning target volume: $\leq$1.2). Moderate dose conformality and gradient quality were controlled by the parameters listed in **TABLE 1**. The treatment plans also had to meet a number of contoured organ dose constraints (**TABLE 2**).

Institutional Review and Accreditation

Prior to enrollment of any patients, sites were required to have both local institutional review board approval and pass central credentialing standards for protocol participation defined by the Advanced Technology Consortium. This credentialing included irradiation of a standard chest phantom (supplied by the Radiologic Physics Center, Houston, Texas). In addition, all sites were required to obtain central approval of their methods of immobilization, motion assessment and control, and target verification. At the time of enrollment of the first patient into the protocol from each center, a central review of the contouring and dosimetry by the primary investigator was facilitated by the Image Guided Therapy QA Center at Washington University (St Louis, Missouri) to ensure that protocol objectives were met.

Follow-up and End Points

Patients were seen every 3 months during years 1 and 2 posttreatment and then every 6 months until 4 years posttreatment; data were analyzed through

August 31, 2009. Imaging with CT scans was required at each visit for response and toxicity assessment. Follow-up PET scans were required if progressive soft tissue abnormalities were noted on the CT scans. Pulmonary function tests (FEV_1, carbon monoxide diffusion, and arterial blood gases) were to be performed every 3 months for year 1 posttreatment and every 6 months for year 2 posttreatment. Tumor measurements at each follow-up were performed using the response evaluation criteria in solid tumors,[12] in which a complete response is total tumor disappearance and partial response is a decrease in the longest tumor diameter by 30% or greater.

The primary end point of the study was 2-year actuarial primary tumor control. Primary tumor control was defined as the absence of primary tumor failure. Primary tumor failure was based on meeting both criteria: (1) local enlargement defined as at least a 20% increase in the longest diameter of the gross tumor volume per CT scan and (2) evidence of tumor viability. Tumor viability could be affirmed by either demonstrating PET imaging with uptake of a similar intensity as the pretreatment staging PET, or by repeat biopsy-confirming carcinoma. Primary tumor failure included marginal failures occurring within 1 cm of the planning target volume (1.5-2.0 cm from the gross tumor volume). Failure beyond the primary tumor but within the involved lobe was collected separately from disseminated failure within uninvolved lobes. Local failure is the combination of the primary tumor and involved lobe failure, with local control being the absence of local failure.

Secondary end points included assessments of treatment-related toxicity, disease-free survival, and overall survival. Disease-free survival included separate assessments of local-regional failure (within the primary site, involved lobe, hilum, or mediastinum) and disseminated recurrence (failure beyond the local and regional sites).

The National Cancer Institute's Common Toxicity Criteria version 3.0 was used for grading adverse events.[13] Certain adverse events attributable to SBRT were specified prospectively within the protocol for use in evaluating the secondary end point of treatment-related toxicity. Specifically, these adverse events included grade 3 measures of lung injury, esophageal injury, heart injury, and nerve damage as well as any grades 4 through 5 toxicity that were related to treatment. However, all adverse events reported by participating centers were collected and assessed.

Statistical Design

The study design aimed to improve the 2-year primary tumor control rate from 60% to 80%. Because conventional radiation provides poor primary tumor control (<40%), a phase 2 study comparing SBRT with conventional radiation would result in a sample size too small for meaningful assessment. Instead, a rate of 60% was chosen as the lowest acceptable primary tumor control rate after taking into consideration the primary tumor control rate of greater than 80% seen in the Indiana University study.[9] Assuming an exponential distribution of time to primary tumor progression, the hazard rate for a primary tumor control rate of 80% was projected to be 0.0093 per month; the hazard rate for a 60% primary tumor control rate was projected to be 0.02128. Eighteen failures were required for a 1-sided type I error rate of .05 with 80% statistical power to detect a difference in primary tumor control rates of at least 20%, resulting in a required sample size of 49 with 2 years of follow-up. After adjusting for a potential ineligibility rate of 5% (based on

Table 1. Dose Gradient Requirements Based on Target Volume for Radiation Therapy Oncology Group 0236[a]

PTV, cm³	Ratio of 50% Prescription Isodose Volume to PTV, $R_{50\%}$		Maximum Dose 2 cm From PTV in any Direction, D_{2cm} (Gy)	
	No Deviation	Minor Deviation[b]	No Deviation	Minor Deviation
1.8	<3.9	3.9-4.1	<28.1	28.1-30.1
3.8	<3.9	3.9-4.1	<28.1	28.1-30.1
7.4	<3.9	3.9-4.1	<28.1	28.1-30.1
13.2	<3.9	3.9-4.1	<28.1	28.1-30.1
21.9	<3.8	3.8-4.0	<30.4	30.4-32.4
33.8	<3.7	3.7-3.9	<32.7	32.7-34.7
49.6	<3.6	3.6-3.8	<35.1	35.1-37.1
69.9	<3.5	3.5-3.7	<37.4	37.4-39.4
95.1	<3.3	3.3-3.5	<39.7	39.7-41.7
125.8	<3.1	3.1-3.3	<42.0	42.0-44.0
162.6	<2.9	2.9-3.1	<44.3	44.3-46.3

Abbreviation: PTV, planning target volume.
[a] Linear interpolation between table entries was required if values of PTV dimension or volume were not specified.
[b] Protocol deviations greater than those listed were classified as major for protocol compliance.

Table 2. Organ Tolerance Dose Limits for Radiation Therapy Oncology Group 0236[a]

Organ	Volume	Total Dose
Spinal cord	Any point	18 Gy maximum
Esophagus	Any point	27 Gy maximum
Ipsilateral brachial plexus	Any point	24 Gy maximum
Heart	Any point	30 Gy maximum
Trachea and ipsilateral bronchus	Any point	30 Gy maximum
Right and left lung	<10% of volume	20 Gy[b]

[a] Exceeding organ limits by more than 2.5% constituted a minor protocol violation and exceeding these organ limits by more than 5% constituted a major protocol violation.
[b] Also known as V-20 or volume of total lung getting 20 Gy or greater.

pretreatment characteristics), the final sample size was 52 patients.

The secondary end point of treatment-related toxicity used the null hypothesis that the toxicity rate is less than or equal to 25% with an overall type I error rate of no more than .10.[14] The null hypothesis would be rejected if there were 17 or more patients with unacceptable toxicity, which was defined as any grade 3 or 4 adverse event related to the symptoms or any grade 4 or 5 adverse event attributed to SBRT, of the first 49 evaluable patients who met all eligibility criteria and received at least some portion of protocol treatment. Three interim analyses of toxicity were planned after 25%, 50%, and 75% of the total number of evaluable patients were accrued.

The hazard rate of primary tumor control at 2 years was estimated using life table estimates with a time span of 2 years. Patients who died within 2 years without primary tumor failure were censored at the time of death. Time of primary tumor control was measured from the start of treatment to the date of tumor failure or date of censoring. A 1-sided z test was used to test the significance between the logarithm of the estimated hazard rate

$$(\lambda_{EST})$$

and the hypothesized hazard rate

$$(\lambda_{hyp} = 0.0093)$$

with a variance equal to the reciprocal of the number of cases with a primary tumor progression observed within 2 years. Thus, the null hypothesis would be rejected at a significance level of .05 when the test statistic z had a value of less than −1.645.

$$Z = \frac{\ln(\lambda_{EST}) - \ln(\lambda_{hyp})}{\frac{1}{\sqrt{Failures}}}$$

Tumor control rates, as well as the secondary end points of disease-free survival and overall survival, were es-timated using the Kaplan-Meier product limit method.[15] A failure for disease-free survival was defined as the first of the following: local failure, marginal failure, regional failure, disseminated recurrence, or death. Patients who were still alive without failure for disease-free survival were censored at the date of last follow-up. A failure for overall survival was death due to any cause; patients who were still alive were censored at the date of last follow-up. All end points were measured from the date of study registration to allow for the risk of toxicity and failure prior to or during SBRT. An unplanned exploratory analysis was performed to examine outcomes within patients with T1 and T2 tumors; no statistical comparisons were performed between these 2 groups. All analyses were performed using SAS software version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Between May 26, 2004, and October 13, 2006, 59 patients were enrolled in the study. Four patients of the 59 enrolled were deemed unevaluable because they did not meet eligibility requirements (3 patients) or did not receive SBRT (1 patient). Pretreatment characteristics for evaluable patients (N=55) appear in **TABLE 3**.

Median follow-up for all evaluable patients was 34.4 months (range, 4.8-49.9 months). Among patients still living (n=29), median follow-up was 38.7 months (range, 30.2-49.9 months). One patient did not return for follow-up evaluations after treatment was completed. It was found through the Social Security Death Index that the patient died 7 months after completion of treatment. This patient was censored for all end points except overall survival for which the patient was reported as a failure. All other patients were able to be evaluated for response at least once. If a patient was not evaluated for disease status at any given follow-up, it was assumed that the disease status reported from the previous follow-up was still applicable. Reasons for a patient not being evaluated were not collected.

Table 3. Pretreatment Characteristics of Patients Enrolled in Radiation Therapy Oncology Group 0236 (N = 55)[a]

| Characteristic	Patients, No. (%)
Age, median (range), y	72 (48-89)
Race/ethnicity	
Asian	2 (4)
Black	2 (4)
White	51 (93)
Sex	
Male	21 (38)
Female	34 (62)
Zubrod performance status score[b]	
0	12 (22)
1	35 (64)
2	8 (15)
Stage	
IA (T1 tumor)	44 (80)
IB (T2 tumor)	11 (20)
Histology	
Squamous cell carcinoma	17 (31)
Adenocarcinoma	19 (35)
Large cell undifferentiated	3 (5)
Non–small cell lung carcinoma not otherwise specified	16 (29)

[a] Unless otherwise indicated.
[b] Defined as fully active, unrestricted for those with a score of 0, restricted activities but able to work for those with a score of 1, and cares for self but unable to work for those with a score of 2.

Digital data submitted to the Image Guided Therapy QA Center was reviewed for contouring and dosimetry compliance. There were no deviations recorded in contouring primary tumor targets. Tumor coverage was scored acceptable for all but 1 patient enrolled (98% tumor coverage compliance). Normal tissue dose constraints were appropriately respected in 40 patients (73% normal tissue dose constraint compliance). There were no reports of using nonprotocol therapy in combination with SBRT.

Twenty-eight patients (51%; 95% confidence interval [CI], 42%-60%) had a complete response occurring a median of 6.5 months (range, 1.6-42.6 months) from completion of SBRT. Partial response was recorded in 21 patients; the rate of complete plus partial response after therapy was 89% (95% CI, 81%-97%).

Only 1 patient (T2N0M0 at diagnosis) experienced a documented recur-

Figure. Patient Course After Initiation of Stereotactic Body Radiation Therapy
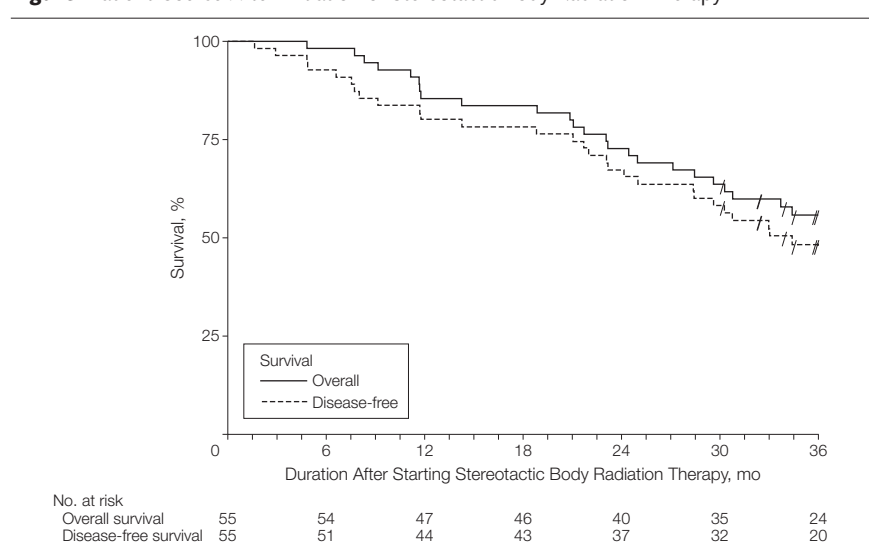
The vertical bars indicate censored observations. The failure rate was 47% for overall survival and 54% for disease-free survival.

rence or progression at the primary site. There were no reported marginal recurrences. The 3-year primary tumor control rate was 97.6% (95% CI, 84.3%-99.7%), with a hazard ratio of 0.001. The corresponding z statistic was –2.226, which was less than –1.645 (P=.01) and was consistent with a hypothesis that the primary tumor control rate would be at least 80%. Three patients had recurrence within the involved lobe; the 3-year primary tumor and involved lobe (local) control rate was 90.6% (95% CI, 76.0%-96.5%).

Regional failures were reported in 2 patients, one occurring at 33.0 months and the other at 36.1 months postprotocol therapy. Combining local and regional failures, the 3-year local-regional control rate was 87.2% (95% CI, 71.0%-94.7%). Disseminated recurrence as some component of recurrence was reported in 11 patients. Collectively, 14 patients had recurrence of cancer. Their patterns of failure included: 1 primary alone, 1 involved lobe alone, 2 involved lobe and disseminated, 1 hilum alone, 1 mediastinum and disseminated, and 8 disseminated alone. The 3-year rate of disseminated failure was 22.1% (95% CI, 12.3%-37.8%) with 8 such failures

occurring prior to 24 months. The 3-year rate of disseminated recurrence for patients with T1 tumors was 14.7% (95% CI, 6.2%-32.7%); however, this rate was 47.0% (95% CI, 22.7%-79.1%) for patients with T2 tumors. The 3-year rates of disseminated recurrence were 5.9% (95% CI, 0.9%-35.0%) for squamous histology and 30.7% (95% CI, 16.8%-51.8%) for nonsquamous histology.

Twenty-six patients died during the period of observation after treatment. Ten patients (18% of entire study population; 95% CI, 8%-23%) died of lung cancer. Two patients died of non–protocol-related medical interventions and 5 of comorbid problems, specifically stroke, myocardial infarction, aggravation of emphysema, and second malignancy. Nine patients died of unknown causes.

Disease-free survival and overall survival at 3 years were 48.3% (95% CI, 34.4%-60.8%) and 55.8% (95% CI, 41.6%-67.9%), respectively (**FIGURE**). Median disease-free survival and overall survival for all patients were 34.4 months (95% CI, 25.0 months to not reached) and 48.1 months (95% CI, 29.6 months to not reached), respectively. For patients with T1 tumors, me-

dian disease-free survival was 36.1 months (95% CI, 25.0 months to not reached) and median overall survival was not reached, which was similar to patients with T2 tumors whose disease-free survival and overall survival were 30.8 months (95% CI, 4.9 months to not reached) and 33.7 months (95% CI, 11.1 months to not reached), respectively.

Seven patients (12.7%; 95% CI, 9.6%-15.8%) and 2 patients (3.6%; 95% CI, 2.7%-4.5%) were reported to experience protocol-specified treatment-related grade 3 and 4 adverse events, respectively. No grade 5 treatment-related adverse events were reported. An additional 6 patients (10.9%; 95% CI, 8.2%-13.6%) were reported to have adverse events attributable to SBRT that were not classified prospectively as protocol specified. Three of these non–protocol-specified adverse events were related to complications of the skin or ribs. All grades of reported SBRT-related adverse events appear in **TABLE 4**. Protocol-specified adverse events only appear in **TABLE 5**. Because only 9 of the first 49 evaluable patients experienced a protocol-specified adverse event, the null hypothesis that the true adverse event rate of 25% or less cannot be rejected.

COMMENT

The main finding in this prospective study was the high rate of primary tumor control (97.6% at 3 years). Primary tumor control is an essential requirement for the cure of lung cancer. Treatments applied for curative intent must be judged at least partly on their ability to control gross disease. Stereotactic body radiation therapy as delivered in RTOG 0236 provided more than double the rate of primary tumor control than previous reports describing conventional radiotherapy.[1,3,16,17] Admittedly, patients deemed medically inoperable have other competing causes of death besides lung cancer.[4] Series reporting results from conventional radiotherapy for similar patient groups report 2-year to 3-year overall survival

Table 4. Adverse Events Related to Stereotactic Body Radiation Therapy[a]

	No. of Patients by Tumor Grade (N = 55)					No. of First Evaluable Patients by Tumor Grade (n = 49)				
	1	2	3	4	5	1	2	3	4	5
Blood or bone marrow	3	1	2	0	0	3	1	2	0	0
Cardiovascular	1	1	0	0	0	1	1	0	0	0
Coagulation	1	0	1	0	0	1	0	1	0	0
Constitutional symptoms	11	8	1	0	0	11	7	1	0	0
Dermatology or skin	3	2	2	0	0	3	1	2	0	0
Gastrointestinal tract	4	1	1	0	0	4	1	1	0	0
Hemorrhage or bleeding	0	2	0	0	0	0	2	0	0	0
Infection	0	1	2	0	0	0	1	2	0	0
Lymphatics	2	0	0	0	0	2	0	0	0	0
Metabolic or laboratory	2	1	1	1	0	2	1	1	1	0
Musculoskeletal or soft tissue	3	5	3	0	0	3	3	3	0	0
Neurology	3	2	1	0	0	3	2	1	0	0
Pain	5	9	0	0	0	5	6	0	0	0
Pulmonary or upper respiratory tract	11	13	8	1	0	11	11	8	1	0
Renal or genitourinary	1	0	0	0	0	1	0	0	0	0
Most severe, No. (%)										
Nonhematologic	13 (24)	17 (31)	13 (24)	2 (4)	0	13 (27)	14 (29)	13 (27)	2 (4)	0
Overall	13 (24)	17 (31)	13 (24)	2 (4)	0	13 (27)	14 (29)	13 (27)	2 (4)	0

[a] Includes adverse events in which relationship to treatment was missing.

rates in the 20% to 35% range,[2,3,18] which are considerably lower than the 55.8% rate at 3 years reported herein.

In contrast to the trial from Indiana University in which the dose levels used in this trial were first piloted,[9] there were no reported SBRT-related patient deaths in RTOG 0236. Perhaps, this is because patients with centrally located tumors were not eligible for RTOG 0236. In contrast, as described in the update by Fakiris et al,[19] the Indiana University experience included 31% of patients with central tumors. They had 5 treatment-related deaths out of the cohort of 70 patients and a 3-year overall survival rate of 42.7%. While we attempted to obtain complete follow-up on all patients, our study was flawed because autopsies were performed on only a few patients at the time of death and 9 patients died of unknown causes.

The most disappointing finding in this trial was the rate of disseminated recurrence (22.1% at 3 years). Because the primary tumor, involved lobe, and regional failure rates were all low and metastases appeared fairly soon after SBRT, it might be assumed that many of these patients harbored occult tumors at diagnosis that went undetected by initial CT and PET

Table 5. Protocol-Specified Adverse Events Related to Stereotactic Body Radiation Therapy[a]

	Patients by Tumor Grade					
	All (N = 55)			First Evaluable (n = 49)		
Adverse Event	3	4	5	3	4	5
FEV$_1$	2	0	0	2	0	0
Hypocalcemia	0	1	0	0	1	0
Hypoxia	2	0	0	2	0	0
Pneumonitis NOS	2	0	0	2	0	0
Pulmonary function test decreased NOS	3	1	0	3	1	0
Maximum for protocol, No. (%)	7 (13)	2 (4)	0	7 (14)	2 (4)	0

Abbreviations: FEV$_1$, forced expiratory volume in the first second of expiration; NOS, not otherwise specified.
[a] Includes adverse events in which relationship to treatment was missing.

staging. Given that the regional failure rate in the hilum and mediastinum was quite low (only 2 patients), adding pre-SBRT hilar or mediastinal pathological staging, as is commonly done in operable patients, would not likely have altered the rate of disseminated recurrence. Instead, these results would imply that either better whole-body staging to identify patients with occult metastatic disease, or effective adjuvant therapies to eradicate such disease are necessary to improve the outcomes.

Because RTOG 0236 was the first North American cooperative group trial using SBRT, considerable effort was ex-

pended in developing the infrastructure to ensure consistent and high-quality treatment across all enrolling centers. The products of these interactions were the compliance criteria, the accreditation and credentialing criteria, the quality assurance assessment criteria and mechanisms, and the data collection and monitoring program all specific to SBRT.[20] This infrastructure greatly facilitated the high compliance observed for this protocol and will eventually allow evaluation of relationships between dosimetry, compliance, and adverse events with longer follow-up (more events) from completed trials.

The RTOG 0236 trial was limited largely by the patient population's ability to undergo invasive procedures. Even the initial biopsy required to confirm malignancy for eligibility was potentially threatening to this frail population. Importantly, the trial did not require and seldom used invasive pathological staging and histological confirmation of recurrence. Rather, noninvasive tests like CT and PET were used; both of which are associated with accuracy problems. Control was consistently evaluated by diagnostic CT scan, but PET was only used if the CT scan showed progressive changes. Collectively, these staging and evaluation methods make this experience difficult to compare with the results after surgical management of healthier patients in which both invasive staging and histological confirmation of recurrence is more common.

The RTOG 0236 trial demonstrated that technologically intensive treatments like SBRT can be performed in a cooperative group so long as the proper infrastructure and support are put in place. The RTOG will be building on RTOG 0236 to (1) design a trial to address the rather high rate of disseminated failure observed after treatment, (2) complete a trial to determine a safe and effective dose for central lung tumors (RTOG 0813), and (3) complete a trial to refine the dose of SBRT for peripheral tumors (RTOG 0915).

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