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Microsimulation Model Predicts Survival Benefit of Radiofrequency Ablation and Stereotactic Body Radiotherapy Versus Radiotherapy for Treating Inoperable Stage I Non–Small Cell Lung Cancer

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Abstract

OBJECTIVE—A subset of patients with stage IA and IB non–small cell lung cancer (NSCLC) is ineligible for surgical resection and undergoes radiation therapy. Radiofrequency ablation (RFA) and stereotactic body radiotherapy are newer potentially attractive alternative therapies.

MATERIALS AND METHODS—We added RFA and stereotactic body radiotherapy treatment modules to a microsimulation model that simulates lung cancer’s natural history, detection, and treatment. Natural history parameters were previously estimated via calibration against tumor registry data and cohort studies; the model was validated with screening study and cohort data. RFA model parameters were calibrated against 2-year survival from the Radiofrequency Ablation of Pulmonary Tumor Response Evaluation (RAPTURE) study, and stereotactic body radiotherapy model parameters were calibrated against 3-year survival from a phase 2 prospective trial. We simulated lifetime histories of identical patients with early-stage NSCLC who were ineligible for resection, who were treated with radiation therapy, RFA, or stereotactic body radiotherapy under a range of scenarios. From 5,000,000 simulated individuals, we selected a cohort of patients with stage I medically inoperable cancer for analysis ($n = 2056$ per treatment scenario). Main outcomes were life expectancy gains.

RESULTS—RFA or stereotactic body radiotherapy treatment in patients with peripheral stage IA or IB NSCLC who were nonoperative candidates resulted in life expectancy gains of 1.71 and 1.46 life-years, respectively, compared with universal radiation therapy. A strategy where patients with central tumors underwent stereotactic body radiotherapy and those with peripheral tumors underwent RFA resulted in a gain of 2.02 life-years compared with universal radiation therapy. Findings were robust with respect to changes in model parameters.

CONCLUSION—Microsimulation modeling results suggest that RFA and stereotactic body radiotherapy could provide life expectancy gains to patients with stage IA or IB NSCLC who are ineligible for resection.

Keywords

comparative effectiveness; lung cancer; radiofrequency ablation; stereotactic body radiotherapy

Surgical resection is the standard of care for early-stage non–small cell lung cancer (NSCLC) and can be curative, with 5-year overall survival rate of 60% and cancer-specific survival rate of 74% [1]. However, 30% of patients with early-stage NSCLC do not undergo surgery because of factors such as advanced age and concomitant illnesses, such as pulmonary disease [2, 3]. Approximately 38% of these patients receive radiotherapy alone, 5% receive chemotherapy, 11% receive chemoradiotherapy, and 12% receive no treatment [2].

Radiofrequency ablation (RFA) is a relatively new treatment that is a potentially curative option for individuals who are ineligible for resection [4–7]. A recent prospective clinical trial of RFA reported 2-year cancer-specific survival rate of 73% in patients with stages I–IV NSCLC and 92% in those with stage I NSCLC [5]. Another study of RFA in patients with stage I NSCLC who were ineligible for surgery reported 3-year cancer-specific survival rate of 87.5% [8]. Though the maximum size for effective treatment is not yet known [5], RFA treatment of tumors smaller than 3 cm has been shown to result in greater disease-free survival rates when compared with treatment of larger tumors [6]. RFA is less effective and generally not considered appropriate for individuals with central tumors proximal (< 1 cm) to the central airways, blood vessels, nerves, and esophagus because of the heatsink effect of large central vessels [9].

Another new treatment option for nonsurgical candidates is stereotactic body radiotherapy. A phase 2 study of stereotactic body radiotherapy reported a 3-year lung cancer-specific survival rate of 82% among patients with stage I NSCLC [10]. Stereotactic body radiotherapy is appropriate for patients with peripheral or central tumors but has been shown to have higher late major airway toxicity in patients with central tumors because of stereotactic body radiotherapy dose and proximity to airways [11, 12]. Stereotactic body radiotherapy, which may require fiducial markers and angled radiation beams, can track the tumor's movement during breathing. As a result, potentially larger doses can be used along with smaller radiation fields, leading to improved effectiveness and reduced complications [11]. Prospective phase 2 trials report 3-year cancerspecific survival rate of 82% [10] and 3-year overall survival rate of 55.8% [13] in patients with inoperable stage IA or IB NSCLC.

Results from preliminary studies of RFA and stereotactic body radiotherapy in patients who are ineligible for surgery can be incorporated into lung cancer simulation models to evaluate the potential long-term comparative effectiveness of treatment and guide the design of future clinical trials. The objective of this study was to estimate the life-years that could be gained by treating a cohort of patients with inoperable stage IA or IB NSCLC with either RFA or stereotactic body radiotherapy instead of radiation therapy by performing a direct comparison of the three treatments. Sensitivity analysis was performed on the parameters specifying treatment effectiveness to identify conditions under which RFA or stereotactic body radiotherapy might be less effective than radiation therapy.

Materials and Methods

The Lung Cancer Policy Model

The Lung Cancer Policy Model is a comprehensive microsimulation of lung cancer development, progression, detection, treatment, and survival. According to risk equations with terms for age, smoking history, sex, and a high-risk marker, individuals can develop up to three lung cancers of five major histologic types. Each cancer is assigned a growth parameter drawn from one of five distributions (corresponding to histologic type) and a location in the lung. The Lung Cancer Policy Model simulates survival as a function of true disease characteristics, such as (current) tumor volume, nodal involvement, and distant metastases, rather than observed stage as assigned by staging tests. Details of the Lung Cancer Policy Model development and calibration are described in an online technical appendix [14].

This study uses only publicly available deidentified human subject data. Smoking histories (start and stop ages and cigarettes per day), derived from survey data, represent a 60-year-old cohort of men and women in 1990. Individuals were assigned as a never, former, or current smoker in 1990. The model assumes an annual baseline rate of 3% smoking cessation for current smokers, but individuals cannot start smoking or relapse after model entry. Cigarettes smoked per day is assumed constant for current smokers.

Simulated Patient Population

The Lung Cancer Policy Model was populated with cohorts of 60-year-old white men and women with smoking histories as described in the previous section. This analysis included patients diagnosed with stage IA or IB NSCLC who are either ineligible for, or who refuse, resection. Because comorbidities are not explicitly modeled, ineligibility was randomly assigned. We assumed that 30% of patients were ineligible for or refused surgery on the basis of reports stating that 25–30% of patients with early-stage NSCLC do not undergo resection [15, 16].

Lung cancer diagnosis could occur via symptom-related or incidental detection on a thoracic imaging examination performed for reasons other than lung cancer (screening was not simulated). Suspicious pulmonary nodules were worked up according to their size at detection. Nodules larger than 8 mm in diameter were biopsied. Nodules up to and including 8 mm in diameter were monitored with serial CT (at months 1, 3, 6, 9, 12, and 24); growth prompted biopsy. Staging examinations followed consensus practice guidelines at the time and included bronchoscopy, needle biopsy, and mediastinoscopy.

Radiation Therapy

The effectiveness of radiation therapy was defined and parameterized as the proportion of cancers with complete (0.23) and partial (0.36) responses [17–19]. A complete radiographic response to radiation therapy was defined as a tumor that was reduced to a diameter of 1.5 mm, or below the limit of detection of a CT examination [20]. A partial response was defined as a tumor that was reduced in diameter by 30% [19]. Cancer growth is simulated using a Gompertz function, where doubling times of tumor growth decrease as tumor size increases.

Model-predicted survival after radiation therapy is expected to be higher than rates observed in similar cohorts in the Surveillance, Epidemiology, and End Results (SEER) database, because the model simulates staging according to consensus practice guidelines that include mediastinoscopy [21]. In the model, patients with stage I or II disease are unlikely to experience the poorer survival associated with N3 disease because mediastinoscopy has high

accuracy. Survival for early-stage lung cancer reported in SEER reflects the low use of preoperative mediastinoscopy and high rates of upstaging at resection [22]. This guideline-only simplification was made because there are few data available on staging practice patterns.

RFA

In the RFA treatment module, resection-ineligible individuals were evaluated for RFA eligibility. Those patients with stage IA or IB NSCLC and who had peripheral tumors 5 cm or smaller were treated with RFA. Patients ineligible for RFA were assigned to radiation therapy. Technical failure was defined as a procedure not performed according to protocol, and without an ablation zone that completely covered the tumor [23]; patients for whom RFA failed in the model were assigned to radiation therapy. The effectiveness of RFA was defined as the percentage of tumors with 100% necrosis and the extent of tumor necrosis in partially destroyed tumors. Among patients for whom RFA is technically successful, the extent of tumor necrosis may vary and depends on tumor size. All patients who undergo RFA are monitored as follows: PET/CT at 1, 6, 12, 24, and 36 months [7] and CT alone at 3, 9, 48, and 60 months. Estimates for the rates of RFA technical failure and effectiveness (based on estimates of partial and complete responses) were derived from two single-center studies [23, 24]. We modeled procedure-related complications, including death. Complication rates were estimated from the literature [7, 9, 23–27] (Table 1).

Stereotactic Body Radiotherapy

In the stereotactic body radiotherapy treatment module, resection-ineligible individuals were evaluated for stereotactic body radiotherapy candidacy. Those patients who had stage IA or IB NSCLC lung cancer and with tumors 5 cm or smaller were treated with stereotactic body radiotherapy. In the base case analysis, only patients with peripheral tumors were considered to allow a direct comparison with RFA. In a sensitivity analysis, we evaluated a scenario in which peripheral and central tumors were treated with stereotactic body radiotherapy [10, 11]. Parameter estimates for stereotactic body radiotherapy effectiveness and complication rates were derived from the results of a phase 2 prospective trial and are listed in Table 1 [10].

Calibration

A sample of patients who were eligible for RFA or stereotactic body radiotherapy was created from the model to reflect the patient characteristics, in terms of tumor size, stage, and type reported in prior trials. Our goal was to generate survival curves that fell within the trials' 95% CIs. For RFA, we randomly sampled from a 50-year-old cohort for comparison with the Radiofrequency Ablation of Pulmonary Tumors Response Evaluation (RAPTURE) study; all patients had stage I NSCLC tumors 3 cm or smaller in diameter. Cancer type was based on the NSCLC sample in RAPTURE, including stage IA or IB and recurrent cancers (40% adenocarcinoma and 55% squamous carcinoma). Using input parameters in Table 1, 1- and 2-year lung cancer-specific survival was found to be 89% and 85%, within the 95% CIs of RAPTURE (78–98% for 1-year and 54–86% for 2-year survival) [5]. Once calibration was completed, local progression was defined as visible growth (≥ 2 mm increase in diameter) of the primary tumor during treatment follow-up and was compared with reported values as a validation check.

Stereotactic body radiotherapy was calibrated against that in the study by Fakiris et al. [10] using input parameters in Table 1. A random sample of patients with stage IA or IB tumors smaller than 5 cm who underwent stereotactic body radiotherapy was created from the 60-year-old cohort and included both central (31%) and peripheral (69%) tumors, in similar proportions to the Fakiris et al. study. Three-year lung cancer-specific survival was

estimated at 78%, consistent with the study by Fakiris et al. (82%; 95% CI, 70–93%). As a validation check, a random sample was created with proportions similar to those in the study by Timmerman et al. [13]. The 3-year overall survival was estimated at 59.5%, comparable to that study's findings (55.8%; 95% CI, 41.6–67.9%) [13].

Base Case Analysis

We compared three treatment strategies for patients with stage IA or IB NSCLC who were ineligible for resection: RFA, stereotactic body radiotherapy, and radiation therapy or current guideline care. In the base case analysis, patients with central cancers or tumors larger than 5 cm in diameter were excluded, on the basis of the low success rates of RFA and stereotactic body radiotherapy for larger tumors and because RFA is not considered appropriate treatment of central tumors. Lifetime histories of a fixed cohort of individuals in each treatment arm were simulated using parallel random number streams [28], so that each treatment arm contained the same individuals for a direct comparison of the treatments. For the base case analysis, 2056 patients matching the inclusion criteria were output from model cohorts of 5,000,000 patients. These patients were treated to create a one-to-one comparison of the three arms. Life-years are presented for each cohort and are discounted at an annual rate of 3% [29].

Sensitivity Analysis

We performed one-way sensitivity analyses on model parameters relating to the effectiveness, morbidity, and mortality of RFA. We considered scenarios in which we changed input parameters for RFA and stereotactic body radiotherapy. In addition, we considered a combined treatment strategy in which patients with central tumors underwent stereotactic body radiotherapy and patients with peripheral tumors underwent RFA, on the basis of the study by Fakiris et al. [10], which showed no significant overall survival difference between patients with peripheral tumors compared with those with central tumors. Note that, because this alternate scenario includes a different case mix of patients, life expectancy gains for the cohort are not directly comparable to the base case results.

Statistical Methods

Survival curves were calculated using the Kaplan-Meier Method. Statistical analyses were performed using SAS software (version 9.1.3, SAS Institute).

Results

Calibration and Validation

The baseline patient population had stage IA or IB lung cancer with the following histologic types: 91% adenocarcinoma, 2% large cell, 4% squamous, and 3% other. The mean tumor size was 1.62 cm (range, 0.1–4.99 cm). Approximately 15% of the cohort never smoked, 68% were former smokers, and 17% were current smokers.

Figure 1 shows the 10-year lung cancer–specific survival rates for each of the treatment strategies. Treatment effectiveness was estimated such that the 2-year cancer-specific survival rate for patients treated with RFA as predicted by the model is 89%, similar to observations for patients with stage I NSCLC in the RAPTURE study (92%; 95% CI, 66–99%) [5]. Three-year cancer-specific survival predicted by the model is 86.4%, and mean local progression-free survival after RFA was 28.46 (SD, 14.50) months. Stereotactic body radiotherapy effectiveness was calibrated such that the 3-year cancer-specific survival rates of patients treated with stereotactic body radiotherapy as predicted by the model is 78% to approximate the observed lung-cancer specific survival rate in the phase 2 study (82%; 95% CI, 70–93%) [10]. Three-year overall survival was 62.6%. The effectiveness of radiation

therapy was not estimated by calibration, but was compared with data from the SEER registry [14]. Survival after radiation therapy as predicted by the model was 90% at 1 year, 53% at 3 years, and 33% at 5 years.

Model Base Case Analysis

The 5-year lung cancer–specific survival rate of the RFA model cohort is 77% versus 73% for stereotactic body radiotherapy and 46% for radiation therapy. At 10 years, the RFA cohort had a mean lung cancer–specific survival rate of 67% versus 61% for stereotactic body radiotherapy and 30% for radiation therapy. Survival curves are presented in Figure 1.

Total life-years for the cohort (Table 2) were 16.20 for RFA, 15.95 for stereotactic body radiotherapy, and 14.49 for radiation therapy, for an increase of 1.71 life-years with RFA and 1.46 life-years with stereotactic body radiotherapy compared with radiation therapy. Women had slightly greater life-year gains (1.72 and 1.49 for RFA and stereotactic body radiotherapy, respectively) than did men (1.69 and 1.44 for RFA and stereotactic body radiotherapy, respectively).

Sensitivity Analysis

RFA and stereotactic body radiotherapy had better lung cancer–specific survival than did radiation therapy in a variety of scenarios, despite uncertainty about model parameters (Table 1) that specify treatment effectiveness. Table 3 shows the life-years gained under these scenarios. In each scenario, RFA and stereotactic body radiotherapy resulted in increased life-years compared with radiation therapy. Reducing the RFA-eligible maximum tumor diameter to 2 cm resulted in an increase of 1.73 life-years compared with radiation therapy. Increasing the rates of partial or complete response to the high parameter estimates (Table 1) with RFA yielded gains of 1.80 and 1.88 life-years, respectively. Decreasing these parameters to the low estimates still yielded life-year gains compared with radiation therapy (1.62 and 1.35 life-years, for partial and complete response, respectively). In the “worst case” scenario, defined as using the low estimates for probability of partial and complete response and the high estimates of complications and mortality found in Table 1, RFA resulted in 1.18 more life-years than did radiation therapy. Under the “best case” scenario (increased probability of partial and complete response), RFA resulted in 2.18 more life-years than radiation therapy.

A combination strategy that included patients with central tumors smaller than 5 cm was considered, and results are presented in Figure 2 and Table 4. Patients with central tumors were eligible for stereotactic body radiotherapy, whereas patients with peripheral tumors were eligible for RFA. Total life-years for the cohort in the RFA or stereotactic body radiotherapy arm were 15.46, compared with 13.44 years for radiation therapy. Life-years are less than the base case results because of inclusion of the patients with central tumors (treated with stereotactic body radiotherapy in the combined strategy). Stereotactic body radiotherapy of central tumors resulted in an increase of 2.21 life-years compared with the same patients treated with radiation therapy.

Discussion

Minimally invasive potentially curative therapies would be welcome alternatives to surgery in older patients with lung cancer who have a high frequency of comorbidities; 46.8% of new diagnoses of NSCLC in 2001 were in patients older than 70 years [30]. Although radiation therapy is considered the standard of care for patients with early-stage NSCLC that is deemed inoperable, it offers only a modest 5-year lung cancer–specific survival increase over no treatment [16]. Using a comprehensive microsimulation model that simulates the

natural history of disease progression of multiple lung cancer histologic types, we predicted 5-year lung cancer-specific survival rates of 77% and 73% for RFA and stereotactic body radiotherapy, respectively, versus 46% for radiation therapy.

By using a model, we evaluated treatments that had not previously been compared directly in a randomized trial, so we verified our model predictions against multiple endpoints. At 2 years, the model-predicted cancer-specific survival rate for patients treated with RFA (89%) was similar to observations in patients with stage I NSCLC reported by Lencioni et al. [5] (92%; 95% CI, 66–99%) and Hiraki et al. [31] (93%; 95% CI, 79–100%). The 3-year cancer specific survival (86.4%) is comparable to the 87.5% observed by Zemlyak et al. [8], and our mean local progression-free survival (28.46 [SD, 14.50] months) is consistent with Lanuti et al. [7] (33 [SD, 3.8] months). For patients treated with stereotactic body radiotherapy, our predicted 3-year overall survival (62.6%) is comparable to those reported by Timmerman et al. [13] (55.8%; 95% CI, 41.65–67.9%) and Ricardi et al. [32] (57.1%). Our model's predicted overall survival after radiation therapy at 1, 3, and 5 years (90%, 53%, and 33%, respectively) was moderately higher than observed in SEER (78%, 45%, and 31%, respectively) [15], likely because of the model's more aggressive staging algorithm and fixed rates of complete and partial responses (see Materials and Methods).

Stereotactic body radiotherapy studies show higher rates of late major airway toxicities, such as pneumonia, apnea, and decreased pulmonary function tests, in patients with central tumors compared with those with peripheral tumors because of the proximity of the tumor to airways [11, 12]. However, despite higher toxicity, overall survival for patients with central tumors was not significantly different [10, 12]. Our model of stereotactic body radiotherapy treatment in patients with stage IA or IB central tumors used parameters reported in these studies [10–12] and suggested that stereotactic body radiotherapy can be an option for these patients, offering a gain of 2.22 life-years compared with treatment with radiation therapy.

Our findings of survival benefits of RFA and stereotactic body radiotherapy over radiation therapy are in line with conclusions from a decision analysis [33] that simulated cohorts from the time of diagnosis and used fixed annual rates of disease progression. Sher et al. [33] did not report life expectancy gains but estimated incremental cost-effectiveness ratios below \$15,000 per quality-adjusted life-year for both stereotactic body radiotherapy and RFA treatment of medically inoperable stage I lung cancer, showing that these treatments are both good values relative to radiation therapy [33].

As with all modeling studies, ours was subject to several limitations. Although competing mortality and lung cancer risks varied with smoking history, comorbidities were not explicitly modeled: the hypothetical patients included in this study were randomly assigned to be nonoperative candidates. However, assigning a comorbidity-specific excess mortality risk (e.g., from chronic obstructive pulmonary disease [COPD]) would affect patients in all treatment arms equally (identical patients were simulated for each treatment arm) and would have no effect on our predicted incremental life expectancy gains attributed to RFA or stereotactic body radiotherapy. Our estimates for absolute life expectancy from any given treatment, however, could be considered upper bounds because patients excluded from resection would be “sicker” than the average patient with stage IA or IB NSCLC. The magnitude of the error is likely to be small, however, because patients with COPD have increased risks of all-cause mortality on the order of a relative risk of 1.4 for stage II COPD to 2.6 for stages III and IV COPD [34]; some of the increase in all-cause mortality reflects increased risk of lung cancer death documented in patients with COPD [35] and some is already accounted for by the model's increased risk of nonlung cancer death due to smoking.

A future analysis would include two advances in lung cancer care: screening (which would affect each treatment arm equally and not change our main conclusion) and intensity-modulated radiation therapy. Because intensity-modulated radiation therapy is still relatively new (i.e., within the past 5–10 years), we thought that a comparator arm of radiation therapy would be more generalizable to the United States.

Limitations resulting from sparse data are worth noting. A scarcity of data on lung cancer and smoking effects in minorities limited this study to U.S. whites. Because of the lack of randomized trials of RFA and stereotactic body radiotherapy, and of studies reporting lung cancer–specific survival rates, calibration targets were limited to one prospective multicenter RFA trial [5] and one phase 2 stereotactic body radiotherapy prospective trial [10]. These trials had a small number of patients (33 [only 13 with stage I disease] and 70, respectively) and short follow-up times (2 years and a median of 4 years, respectively); therefore, results may not be generalizable. However, we performed a number of sensitivity analyses, and conclusions were robust despite these uncertainties.

Limitations of the model include overprediction of survival with radiation therapy treatment when compared with SEER; thus, gains from RFA or stereotactic body radiotherapy treatment would be higher than reported here, and our overall conclusions do not change. The Lung Cancer Policy Model [14] includes parameters that allow faster-growing cancers to respond differently to treatment but simplifies the treatment response by assigning fixed reductions in size for partial or complete responses to radiation therapy. Allowing a range of size reductions (e.g., 0–29% for “no response”) would add noise but not necessarily accuracy for prediction of survival, because response rates are known to be poor predictors of survival [17]. Genomic profiling of tumors is likely to be a better prognostic tool than radiographic response rate.

Our analysis predicted average gains in survival and life expectancy and was not designed to inform treatment decisions at the individual patient level. For patients with stage IA or IB NSCLC with contraindications to surgery, the choice between RFA and stereotactic body radiotherapy will depend on characteristics we accounted for in our analysis, such as lung tumor size and location and comorbidities, but also individual patient preferences and treatment availability. For example, patients with cardiopulmonary compromise may find it difficult to remain motionless for stereotactic body radiotherapy treatment sessions [36]; therefore, RFA may be a better option because of its single treatment session. Alternatively, it may be difficult to place the RFA electrode in certain tumors (e.g., tumors close to the scapula) [37], favoring stereotactic body radiotherapy. On the other hand, stereotactic body radiotherapy may be less desirable when fiducial markers are required because of a risk for pneumothorax that is similar to that for RFA. RFA and stereotactic body radiotherapy also offer several procedure advantages over radiation therapy, in addition to survival gains. Radiation therapy is administered in multiple fractions (requiring multiple patient visits). In contrast, RFA often requires only a single treatment session and spares adjacent normal lung [7]. Stereotactic body radiotherapy requires multiple treatment visits, although fewer on average than radiation therapy, and offers the advantage of targeting lung tumors more efficiently through its ability to track tumor movement during breathing, sometimes with the use of fiducial markers and angled radiation beams.

Although our analysis focused on patients with early-stage NSCLC, RFA may also be a promising option for patients with lung cancer who cannot undergo surgery because of advanced disease. A study by de Baère et al. [38] observed an 18-month overall survival rate of 71% in patients treated with RFA for lung metastases. Treatment with RFA for selective groups of single-lung patients after pneumonectomy resulted in 2-year overall survival rates of 71.4% [39] and 59% [40].

In summary, our model results suggest that RFA and stereotactic body radiotherapy could provide life expectancy gains (relative to radiation therapy) for patients with stage IA or IB NSCLC who are ineligible for resection, with RFA providing the greatest life expectancy gain among patients with peripheral tumors. However, a direct comparison of RFA and stereotactic body radiotherapy in a randomized clinical trial is needed to assess long-term survival rates before a change in treatment policy can be introduced.

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Fig. 1. Product-limit survival estimates for radiofrequency ablation (RFA) versus stereotactic body radiotherapy versus radiation therapy in patients with peripheral tumors.

Fig. 2. Product-limit survival estimates for radiofrequency ablation (RFA) and stereotactic body radiotherapy versus radiation therapy in patients with stage IA or IB non-small cell lung cancer.

TABLE 1

Module Input Parameters

Parameter	Base Case Estimates		Sensitivity Analysis Estimates		
	Estimate (%)	Source	Low Estimate (%)	High Estimate (%)	Source
RFA treatment					
Technical failure	2.5	[23]	2	12	Calibration
Probability of complete response					
Tumors 2 cm (stage IA)	70	[23,24]	50	90	[27]
Tumors > 2 and 3 cm (stage IA)	50	[23]	30	60	[25]
Tumors > 3 and 5 cm (stage IB)	30	[23,24]	10	40	[23,25]
Probability of partial response					
Tumors 2 cm (stage IA)	70	[5], Calibration	50	90	[5], Calibration
Tumors > 2 and 3 cm (stage IA)	50	[5], Calibration	30	70	[5], Calibration
Tumors > 3 and 5 cm (stage IB)	30	Calibration	10	50	Calibration
Morbidity and mortality					
Minor complications (e.g., pneumothorax requiring observation)	15	[23]	5	35	[23,27]
Major complications (requiring inpatient hospitalization)	7	[9,23,27]	4	15	[25]
Operative mortality (% of all patients undergoing RFA)	0.4	[25]	0	6	[26]
Stereotactic body radiotherapy treatment					
Probability of complete response					
Tumors 2 cm (stage IA)	60	[10], Calibration ^a	40	80	[10], Calibration
Tumors > 2 and 3 cm (stage IA)	40	[10], Calibration	20	60	[10], Calibration
Tumors > 3 and 5 cm (stage IB)	20	[10], Calibration	10	30	[10], Calibration
Probability of partial response					
Tumors 2 cm (stage IA)	60	[10], Calibration	40	80	[10], Calibration
Tumors > 2 and 3 cm (stage IA)	40	[10], Calibration	20	60	[10], Calibration
Tumors > 3 and 5 cm (stage IB)	20	[10], Calibration	10	40	[10], Calibration
Morbidity and mortality					
Minor complications, peripheral (e.g., pneumonia requiring observation)	11	[10]	5	35	[27]
Minor complications, central (e.g., pneumonia requiring observation)	23	[10]	10	35	[27]
Major complications, peripheral (requiring inpatient hospitalization) and	7	[10]	4	15	[10], Calibration

Parameter	Base Case Estimates		Sensitivity Analysis Estimates		
	Estimate (%)	Source	Low Estimate (%)	High Estimate (%)	Source
central (requiring inpatient hospitalization)					
Operative mortality	0.4	[10], Calibration	0	6	[10], Calibration

Note—RFA = radiofrequency ablation.

^aSee text for calibration methods.

TABLE 2

Treatment of Stage IA and IB Peripheral Non–Small Cell Lung Cancer Tumors

Patient Group, Therapy	Total Life Expectancy (y)	Incremental Life Expectancy Compared With Radiotherapy (y)
Men		
Radiation therapy	13.96	
Stereotactic body radiotherapy	15.40	1.44
Radiofrequency ablation	15.65	1.69
Women		
Radiation therapy	15.06	
Stereotactic body radiotherapy	16.55	1.49
Radiofrequency ablation	16.78	1.72
All patients		
Radiation therapy	14.49	
Stereotactic body radiotherapy	15.95	1.46
Radiofrequency ablation	16.20	1.71

Note—Data are total and incremental life expectancy for each cohort, for radiotherapy compared with radiofrequency ablation or stereotactic body radiotherapy (discounted by 3%).

TABLE 3

Sensitivity Analysis of Peripheral Non–Small Cell Lung Cancer Tumor Treatment Compared With Radiotherapy

Scenario	Radiotherapy Total Life Expectancy (y)	Stereotactic Body Radiotherapy Incremental Life Expectancy (y)	Radiofrequency Ablation Incremental Life Expectancy (y)
Base case scenario	14.49	1.46	1.71
Tumors 3 cm only	14.64	1.56	1.81
Tumors 2 cm only	15.11	1.55	1.73
Reduced complete response	14.47	1.28	1.35
Increased complete response	14.47	1.85	1.88
Reduced partial response	14.47	1.33	1.62
Increased partial response	14.47	1.54	1.80
Worst ^a	14.51	0.90	1.18
Best ^b	14.47	1.91	2.18

^aReduced partial and complete response, increased complication, and mortality are based on estimates in Table 1.

^bIncreased partial and complete response are based on estimates in Table 1.

TABLE 4

Sensitivity Analysis of Treatment of Central (Stereotactic Body Radiotherapy) and Peripheral (Radiofrequency Ablation) Tumors Compared With Universal Radiation Therapy

Scenario	Radiation Therapy Total Life Expectancy (y)	Radiofrequency Ablation (Peripheral) and Stereotactic Body Radiotherapy (Central) Incremental Life Expectancy (y)
Base case scenario	13.44	2.02
Tumors 3 cm only	13.47	2.08
Tumors 2 cm only	13.71	2.09
Reduced complete response	13.44	1.52
Increased complete response	13.45	2.51
Reduced partial response	13.45	1.88
Increased partial response	13.44	2.06
Worst ^a	13.94	1.23
Best ^b	13.45	2.54

^aReduced partial and complete response, increased complication, and mortality are based on estimates in Table 1.

^bIncreased partial and complete response are based on estimates in Table 1.