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CLINICAL INVESTIGATION

COST-EFFECTIVENESS ANALYSIS OF STEREOTACTIC BODY RADIOTHERAPY AND RADIOFREQUENCY ABLATION FOR MEDICALLY INOPERABLE, EARLY-STAGE NON–SMALL CELL LUNG CANCER

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Purpose: The standard management of medically inoperable Stage I non–small-cell lung cancer (NSCLC) conventionally has been fractionated three-dimensional conformal radiation therapy (3D-CRT). The relatively poor local control rate and inconvenience associated with this therapy have prompted the development of stereotactic body radiotherapy (SBRT), a technique that delivers very high doses of irradiation typically over 3 to 5 sessions. Radiofrequency ablation (RFA) has also been investigated as a less costly, single-day therapy that thermally ablates small, peripheral tumors. The cost-effectiveness of these three techniques has never been compared.

Methods and Materials: We developed a Markov model to describe health states of 65-year-old men with medically inoperable NSCLC after treatment with 3D-CRT, SBRT, and RFA. Given their frail state, patients were assumed to receive supportive care after recurrence. Utility values, recurrence risks, and costs were adapted from the literature. Sensitivity analyses were performed to model uncertainty in these parameters.

Results: The incremental cost-effectiveness ratio for SBRT over 3D-CRT was $6,000/quality-adjusted life-year, and the incremental cost-effectiveness ratio for SBRT over RFA was $14,100/quality-adjusted life-year. One-way sensitivity analysis showed that the results were robust across a range of tumor sizes, patient utility values, and costs. This result was confirmed with probabilistic sensitivity analyses that varied local control rates and utilities.

Conclusion: In comparison to 3D-CRT and RFA, SBRT was the most cost-effective treatment for medically inoperable NSCLC over a wide range of treatment and disease assumptions. On the basis of efficacy and cost, SBRT should be the primary treatment approach for this disease. © 2011 Elsevier Inc.

Stereotactic radiation therapy, Inoperable lung cancer, Cost-effectiveness analysis.

INTRODUCTION

The traditional treatment for medically inoperable, early-stage non–small-cell lung cancer (NSCLC) conventionally has been fractionated radiation therapy (RT) (1). The dose per day with this treatment is typically 1.8 to 2 Gy per fraction, and the total dose ranges between 60 and 70 Gy. Although conventional RT takes 6 to 8 weeks to complete, the results are disappointing, with local control rates hovering between 50% and 70% (2–4). During the earlier era in which these doses were established, radiation portals were designed via fluoroscopy, a relatively unsophisticated imaging modality with poor resolution of tumor and normal tissue anatomy. Radiotherapy fields needed to be large to ensure that the entire tumor was irradiated, and this limited the total amount of radiation that could be delivered. More recently, computed tomography–based planning has been used, such that the radiation plan is created by use of three-dimensional information, a process called three-dimensional conformal radiotherapy (3D-CRT). This more robust imaging technique and planning software prompted radiation dose–escalation studies, whose goals were to improve treatment efficacy while maintaining similar complication rates. These dose-escalation regimens consisted of the same dose of irradiation per day as standard radiotherapy but increased the number of treatments by several weeks. Unfortunately, despite the additional radiation dose, the local control rates were generally still poor, although recently, Phase III data in locally advanced lung cancer have suggested a survival benefit to dose escalation (4–6).

These relatively unsuccessful outcomes have catalyzed the development of other nonsurgical therapies for this disease. Over the past 10 years, stereotactic body radiotherapy (SBRT) has been established, a technique in which very high doses of irradiation—usually 12 to 18 Gy per fraction—are delivered in typically 3 to 5 sessions. SBRT has been shown to dramatically reduce local failure while

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achieving low toxicity rates because of extremely tight expansion margins around the primary tumor (7). In addition, radiofrequency ablation (RFA), which uses a percutaneous catheter to thermally treat the tumor, has shown promise in eradicating Stage I NSCLC (1).

The costs associated with conventional 3D-CRT, SBRT, and RFA vary substantially. RFA is the least expensive treatment modality, whereas SBRT is the most costly, and 3D-CRT is in between the two. Given the differences in efficacy between these three treatments, as well as the nontrivial discrepancy in cost, the cost-effectiveness of these three treatments is an important consideration in deciding which therapy should be implemented for medically inoperable, early-stage NSCLC.

Cost-effectiveness analysis is a proven analytic technique that assesses the relative benefit of a given treatment strategy, quantified in quality-adjusted life-years (QALYs), vs. its cost (8). We have performed a cost-effectiveness analysis of nonsurgical treatments of medically inoperable, early-stage NSCLC, comparing conventional RT, SBRT, and RFA.

METHODS AND MATERIALS

Decision model

We designed a Markov model to simulate the clinical history of a 65-year-old man with medically inoperable Stage I NSCLC (Fig. 1). Markov simulation allows hypothetical cohorts of patients to transition between different health states in fixed increments of time (9).

Patients began in the well state (no evidence of disease [NED]) having received either 3D-CRT, SBRT, or RFA. These health states were titled 3D-CRT–NED, SBRT–NED, and RFA–NED (Fig. 1). Patients then remained in the NED health states or proceeded to the disease states, including local recurrence, regional recurrence, and distant metastasis. Patients could remain in that disease state or die of disease. By definition, this patient population is quite frail (*i.e.,* could not tolerate surgery), and therefore aggressive salvage therapy was not considered to be a feasible option; instead, patients were given best supportive care at any recurrence (10). Patients could die of other causes at any state in the model.

Patients who received 3D-CRT or SBRT were exposed to a risk of pneumonitis between 3 and 6 months after finishing RT. Grade 2 pneumonitis was treated with prednisone and assumed to last for 3 months, whereas Grade 3 pneumonitis was treated with prednisone and home oxygen for 6 months. Patients with pneumonitis were assumed to visit their physician monthly for evaluation. Significant chest wall pain is a unique complication of SBRT, and patients treated with this modality could transition to the chest wall pain health state between 6 and 12 months (11). The condition was assumed to be self-limited and treated with narcotics (*i.e.,* oxycodone). The rate of pneumothorax requiring chest tube and hospital admission after RFA was obtained from the literature (12, 13). All patients with pneumonitis or a pneumothorax underwent an additional chest computed tomography scan with contrast as a follow-up examination.

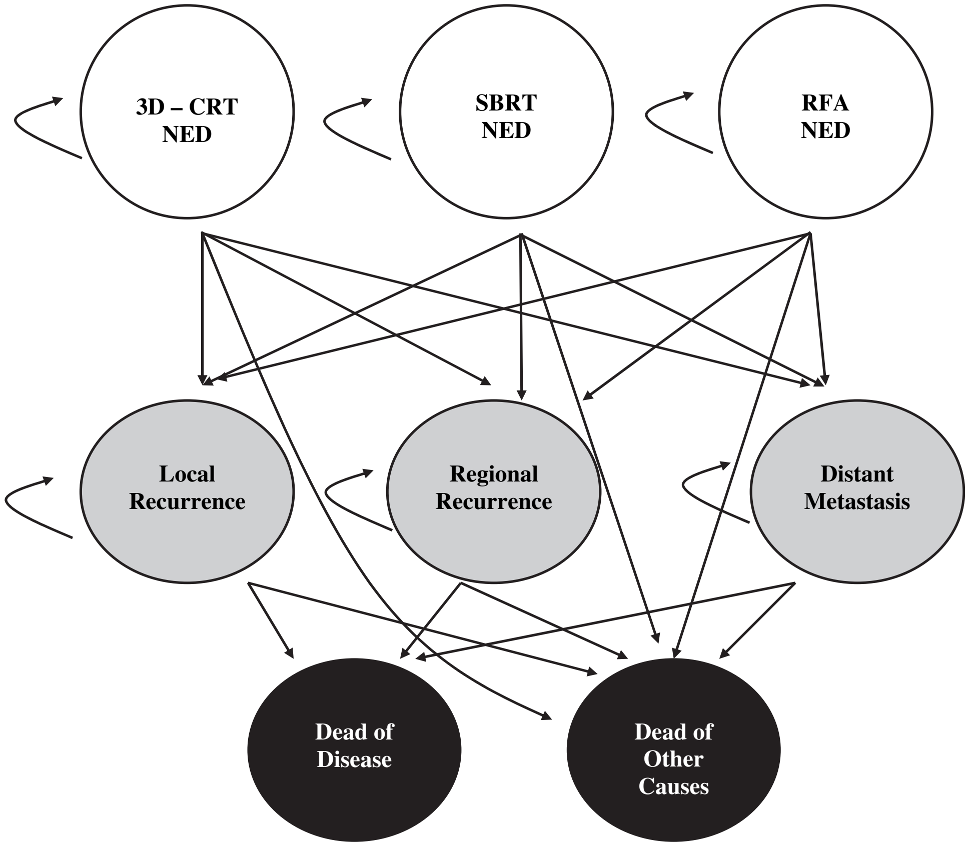

Fig. 1. Markov model describing health states after treatment for early-stage non–small-cell lung cancer. 3D-CRT = three-dimensional conformal radiation therapy; NED = no evidence of disease; SBRT = stereotactic body radiotherapy; RFA = radiofrequency ablation.

A lifetime time horizon was used in the model, although the vast majority of the cohort was deceased by 5 years after treatment. The model was created and analyzed by use of Data TreeAge Pro (TreeAge Software, Williamstown, MA).

Model assumptions and data

Data sources for the decision model are shown in Table 1. All probabilities were extracted from the published literature and calibrated for consistency with established studies evaluating the three techniques. We kept the rates of regional recurrence and distant metastasis as a first failure the same across treatment modalities, because nodal spread and distant spread should have occurred before treatment and are therefore unrelated to how the primary cancer is treated. Thus, the difference in cancer outcomes after treatment with 3D-CRT, SBRT, and RFA was strictly a function of differences in their respective local control rates. The local recurrence rate for SBRT treatment was derived from long-term follow-up data from the Indiana University Phase II SBRT trial, which has the longest follow-up of any prospective SBRT trial (7). Local recurrence rates after treatment with RFA were obtained from data from Brown University, which has published the largest experience using the technique (12). The conventional radiotherapy model was derived from data from Washington University and Duke University from two well-known series reporting outcomes using conventional RT (2, 3).

Costs accrued in each health state were largely derived from publicly available 2009 Medicare payment schedules (Table 2). Costs of end-of-life care as a consequence of a cancer-related death or a non–cancer-related death were taken from a Medicare study published by Campbell *et al.* (14). Patients in whom Grade 2 radiation pneumonitis and chest wall pain developed were treated with prednisone and oxycodone, respectively, and the costs of treatment with these medications were obtained from *Red Book* (15). Costs for patients with Grade 3 pneumonitis who require home oxygen therapy were obtained from a study evaluating these costs in the Medicare population (16). Patients with any pneumonitis were seen every month by the physician and billed for that visit (*i.e.,* Common Procedural Terminology code 99214, intermediate-level established patient visit for management). The cost of inserting and managing the complication of iatrogenic pneumothorax was obtained from the reimbursement for Diagnosis Related Group 200, Complicating Condition (pneumothorax with non-major comorbidity) (17). The cost of the chest computed tomography scan was taken from the Medicare reimbursement for the examination (18). A payer perspective was used in this analysis.

There are no data explicitly evaluating patient utility values after treatment with SBRT, 3D-CRT, or RFA. However, Doyle *et al.* (19) published a study that elicited patient utility values after several health care states associated with NSCLC. These values were used in this study and tested in sensitivity analyses.

Table 1. Probabilities, utility values, and costs used in study

Event	Baseline value	Range studied	Reference
Probabilities			
NED to local recurrence			
3D-CRT	37% (3 y)	20–85%	2
SBRT	12% (3 y)	5–20%	7
RFA	43% (3 y)	10–75%	12
NED to nodal recurrence	9% (2 y)	5–15%	7
NED to metastasis	13% (3 y)	5–25%	7
Nodal recurrence to death	70% (1 y)	50–100%	10
Local recurrence to death	70% (1 y)	50–100%	10
Distant metastasis to death	70% (1 y)	50–100%	10
Pneumothorax rate (RFA only)	16%	0–26%	12, 13
Chest wall pain probability (SBRT only)	20%	—	10
Grade 2 pneumonitis rate (SBRT only)	24%	—	21
Grade 3 pneumonitis rate (SBRT only)	12%	0–20%	21
Utility values			
NED	0.712	0.6–0.95	19
Pneumonitis	0.576	0.461–0.712	19
Chest wall pain	0.557	0.461–0.712	19
Local, nodal, and distant recurrence	0.461	0.2–0.576	19
Death	0	0	19
Costs			
Pneumothorax	$5,401.13	$3,000–$7,500	17
Chest wall pain	$24.82/mo	—	15, 18
Grade 2 pneumonitis	$90.25/mo	—	15
Grade 3 pneumonitis (one-time oxygen equipment cost, monthly cost)	$1,371.32, $272.44/mo	—	15, 16, 18
Chest CT scan	$379.10		18
Palliative care (for any recurrence)	$42,236.49	$10,000–$50,000	14
Non-cancer end-of-life care	$36,609.08	$10,000–$50,000	14

Abbreviations: NED = no evidence of disease; 3D-CRT = three-dimensional conformal radiation therapy; SBRT = stereotactic body radiotherapy; RFA = radiofrequency ablation; CT = computed tomography.

Costs are expressed in 2009 US dollars.

Table 2. Costs associated with 3D-CRT, SBRT, and RFA

Activity	CPT/HCPCS	Description	No.	ASC	OPPS	MPFS	Subtotal
SBRT							
Simulation	77290	Simulation—complex	1		$255.69	$78.26	$333.95
	77334	Immobilization device—complex	1		$188.16	$62.03	$250.19
Physician planning	77263	Clinical treatment planning—complex	1		—	$158.33	$158.33
	77470	Special treatment procedure	1		$373.21	$104.95	$478.16
Physics plan	77295	Three dimensional planning	1		$892.90	$228.66	$1,121.56
	77300	Dosimetry calculation	7*		$114.70	$31.02	$1,020.04
	77334	Treatment device—complex	7*		$188.16	$62.03	$1,751.33
Treatment	G0339	Stereo body robotic treatment (first)	1		$3,803.23	—	$3,803.23
	G0340	Stereo body robotic treatment (second–third)	2		$2,579.82	—	$2,579.82
Treatment management	77435	Stereotactic body treatment management	1		—	$664.70	$664.70
SBRT total					$14,741.13		
3D-CRT							
Simulation	77290	Simulation—complex	1		$255.69	$78.26	$333.95
	77334	Immobilization device—complex	1		$188.16	$62.03	$250.19
Physician planning	77263	Clinical treatment planning—complex	1		—	$158.33	$158.33
	77470	Special treatment procedure	1		$373.21	$104.95	$478.16
Physics plan	77295	Three dimensional planning	1		$892.90	$228.66	$1,121.56
	77300	Dosimetry calculation	5*		$114.70	$31.02	$728.60
	77334	Treatment device—complex	5*		$188.16	$62.03	$1,250.95
Treatment	77413	Radiation treatment delivery (6–10 MV)—complex	35		$152.05	—	$5,321.75
Treatment management	77427	Radiation treatment management	7		—	$188.26	$1,371.28
3D-CRT total					$11,014.77		
RFA							
	32998	Ablation therapy for eradiation of pulmonary tumor		$2054.92	$3071.83	$330.14	$5681.85
	77013	CT image guidance		—	—	$197.77	$197.77
RFA total					$5,879.62		

Abbreviations: 3D-CRT = three-dimensional conformal radiotherapy; SBRT = stereotactic body radiotherapy; RFA = radiofrequency ablation; CPT = Common Procedural Terminology; HCPCS = Healthcare Common Procedure Coding System; MPFS = Medicare physician fee schedule; OPPS = outpatient prospective payment system; ASC = ambulatory surgical center; CT = computed tomography.

All costs are expressed in 2009 US dollars.

* Assumes 5 or 7 treatment fields.

Sensitivity analyses

Sensitivity analyses evaluate the effect of adjusting the assumptions of the model. We performed a wide range of one-way sensitivity analyses for the parameters listed in Table 1. When one strategy was both more effective (higher QALYs) and less costly, that strategy is described as "dominating" the other strategies. If a therapeutic approach is more effective but also more costly, the incremental cost-effectiveness ratio (ICER) is described.

The intuitive and apparent sensitivity of the results to the local control rates of the three treatments prompted a two-way sensitivity analysis, in which the parameters listed in Table 1 were varied while we also changed the assumed control rate of the therapies. Because tumor control for each treatment is proportional to tumor volume, for small, T1 cancers (assumed to be 2 cm), we assumed the best local control rates reported in the literature for each modality: SBRT, 94% at 2 years (Radiation Therapy Oncology Group [RTOG] 0236); 3D-CRT, 81% at 2 years; and RFA, 88% at 1 year (RAPTURE [Radiofrequency Ablation of Pulmonary Tumors Response Evaluation] trial) (2, 13, 20, 21). To estimate the efficacy of treating larger T2 tumors, we used local control rate data from series that reported results stratified by tumor size: SBRT, 78% at 3 years; 3D-CRT, 40% at 3 years; and RFA, 24% at 3 years (2, 12, 22).

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) is a technique in which unknown parameters are assigned a probability distribution according to prior data and Monte Carlo simulations are performed, in which the value of the unknown parameter(s) is drawn from those distributions. If the resulting ICER of the more effective strategy is less than the societal willingness to pay (WTP), then that iteration is considered cost-effective. This result is graphed on an acceptability curve, which reports the percentage of iterations in which a strategy is cost-effective at a series of societal WTP values.

We performed a PSA that varied efficacy of 3D-CRT, SBRT, and RFA, as well as utility values of the NED and recurrence health states. The probability distributions were created by use of a triangular distribution function, in which the most likely, minimum, and maximum values are specified. The most likely value was the value used in the base-case analysis. The input distributions were structured as follows: 3D-CRT efficacy (minimum local failure rate, 20%; most likely, 37%; and maximum local failure rate, 80%); SBRT efficacy (5%, 12%, and 20%, respectively); RFA efficacy (10%, 43%, and 60%, respectively); utility value for NED health state (0.6, 0.712, and 0.95, respectively); and utility value for recurrent health state (0.461, 0.5, and 0.712, respectively).

Discounting

Both costs and QALYs were discounted at an annual rate of 3%. The concept of discounting accounts for the fact that money today is equal to more money in the future (an idea comparable but not identical to an interest rate) and, similarly, that a given health status today is equal to a higher health status in the future. There are additional theoretic reasons why QALYs need to be discounted in a cost-effectiveness analysis, which are beyond the scope of this analysis (23).

RESULTS

Model validity

This model was validated for each treatment modality. The model predicted 3-year local recurrence, regional recurrence, and distant metastasis rates for patients undergoing SBRT of 10.5%, 9%, and 9%, respectively, which echoes the Indiana University–reported rates of 12%, 9%, and 13%, respectively (7). The model predicted 3- and 5-year overall survival rates of 44% and 20%, respectively, which compares well with the Indiana University data (43% and 15%, respectively). For patients undergoing 3D-CRT, the model predicted 3-year local recurrence, regional recurrence, and distant metastasis rates of 34%, 7%, and 7%, respectively, which are quite comparable to the findings from Bradley *et al.* (2) of 37%, 13%, and 19%, respectively; it is notable that the latter number on metastatic disease included cumulative incidence of metastasis (rather than first failure). The predicted 3- and 5-year overall survival rates were 31% and 12%, respectively, results similar to those of Bradley *et al.* and Sibley *et al.* (3), which reported 3- and 5-year overall survival rates of 34% and 13%, respectively (Bradley *et al.* did not report 5-year results). Finally, the model showed that patients undergoing RFA had a predicted 3-year local recurrence rate of 40%, similar to data from Simon *et al.* (12), which found a rate of 43% for tumors less than 3 cm. The predicted 3-year overall survival rate was 29%, which is similar to the data from Simon *et al.*, with a 3-survival rate of 36%. The 5-year survival rates were moderately different: the model predicted a rate of 10% vs. 27%. Long-term survival is also dependent on underlying comorbidities, which could explain the difference. Thus, in summary, these results strongly suggest that our model emulates the actual disease processes after treatment with any of these modalities.

Base case

In the base-case analysis, RFA, 3D-CRT, and SBRT were associated with a mean cost per quality-adjusted life-expectancy of $44,648/1.45, $48,842/1.53, and $51,133/1.91, respectively. The ICER of 3D-CRT over RFA was $52,400/QALY. However, the ICER of SBRT over 3D-CRT was $6,000/QALY, and thus the ICER of SBRT over RFA was $14,100/QALY. In other words, if all three treatment options are available to the clinician, in the base case, SBRT is clearly the most cost-effective treatment, whereas if SBRT delivery is not feasible, RFA is the next most cost-effective option.

One-way sensitivity analyses

A series of 1-way sensitivity analyses were performed, the results of which are shown in Table 3. In almost any

Table 3. One-way sensitivity analyses

Parameter	Range studied	ICER Lower bound	ICER Upper bound
Probabilities			
NED to local recurrence			
3D-CRT	20–80%	SBRT ($29,700/Q)	SBRT ($14,100/Q)
SBRT	5–25%	SBRT ($10,200/Q)	SBRT ($40,300/Q)
RFA	10–75%	RFA (dominant*)	SBRT ($6,000/Q)
NED to nodal recurrence	5–15%	SBRT($12,500/Q)	SBRT ($17,200/Q)
NED to metastasis	5–25%	SBRT ($12,000/Q)	SBRT ($18,700/Q)
Recurrence to death	50–100%	SBRT ($14,400/Q)	SBRT ($11,100/Q)
SBRT Grade 3 pneumonitis rate	5–20%	SBRT ($13,200/Q)	SBRT ($16,200/Q)
Pneumothorax rate	0–26%	SBRT ($16,100/Q)	SBRT ($12,800/Q)
Utility values			
NED	0.6–0.95	SBRT ($15,100/Q)	SBRT ($13,500/Q)
Pneumonitis	0.461–0.712	SBRT ($17,500/Q)	SBRT ($11,600/Q)
Chest wall pain	0.461–0.712	SBRT ($14,100/Q)	SBRT ($14,100/Q)
Recurrence	0.2–0.576	SBRT ($13,000/Q)	SBRT ($15,100/Q)
Costs			
3D-CRT	$5,000–$15,000	SBRT ($21,900/Q)	SBRT ($14,100/Q)
BRT	$10,000–$20,000	SBRT ($25,500/Q)	SBRT ($3,800/Q)
RFA	$3,000–$12,000	SBRT ($20,400/Q)	SBRT ($800/Q)
Palliative care	$10,000–$50,000	SBRT ($30,700/Q)	SBRT ($10,100/Q)
Non-cancer end-of-life care	$10,000–$50,000	SBRT ($3,200/Q)	SBRT ($19,600/Q)

Abbreviations: ICER = incremental cost-effectiveness ratio; NED = no evidence of disease; 3D-CRT = three-dimensional conformal radiotherapy; SBRT = stereotactic body radiotherapy; RFA = radiofrequency ablation; Q = quality-adjusted life-year.

* Refers to a strategy that is more effective and less costly than the baseline strategy.

scenario, SBRT was the most cost-effective option, with ICER values generally less than $25,000/QALY, which is well under most accepted societal WTP values (8). It is important to note that RFA dominated the other two strategies when its associated 3-year risk of local recurrence was only 10% while keeping the local recurrence risks of SBRT and 3D-CRT at 12% and 37%, respectively. This result prompted a two-way sensitivity analysis, in which one tested parameter was tumor size, because size is strongly correlated with success rates in both radiotherapy and RFA.

Two-way sensitivity analyses

Two-way sensitivity analyses were used to estimate the cost-effectiveness of these treatments for small (T1, estimated at 2 cm in diameter) and large (T2, estimated at 4 cm) primaries, and the results are shown in Table 4. When only the size was varied, SBRT was cost-effective for both T1 (ICER of SBRT over RFA of $30,400/QALY) and T2 cancers (ICER of SBRT over 3D-CRT of $3,900/QALY). Even for T1 malignancies, in which the other two less-costly treatments themselves result in increased local control, SBRT (assumed to have a 2-year local control rate of 94% per RTOG 0236) was almost always the most cost-effective treatment; this result held true even when the utility values were widely varied, suggesting that the result is not sensitive to patient preferences. It is notable that if the cost of SBRT was $20,000 (significantly higher than Medicare reimbursement) or the cost of palliative care was only $10,000 (significantly lower than suggested in the literature), RFA was the most cost-effective strategy at a societal WTP of $50,000/QALY: the ICERs of SBRT over RFA were $52,300/QALY and $51,700/QALY for the more expensive SBRT and less expensive palliative care analyses, respectively. Although the local control rates for all 3 modalities decrease with T2 tumors, the drop is significantly less with SBRT, and thus SBRT was always the most cost-effective therapy in treating these larger tumors.

It is also worth noting that holding other variables constant, the ICER for 3D-CRT over RFA was $107,000/QALY for small tumors but $6,800/QALY for larger tumors, again showing that RFA is the cost-effective treatment option for small—but not large—peripheral NSCLCs in which SBRT is not available.

Probabilistic sensitivity analysis

The PSA is shown in Fig. 2. The varied parameters included the efficacy of 3D-CRT, SBRT, and RFA, as well as the utility values of the NED and recurrence health states. The probability that SBRT was cost-effective at a societal WTP of $50,000/QALY was 70%, and in fact, SBRT was cost-effective in the majority of the trials once the WTP exceeded only $30,000/QALY. These results further support the cost-effectiveness of SBRT over a wide range of assumptions.

DISCUSSION

We have shown that, given previously published data, SBRT is the most cost-effective treatment for medically inoperable Stage I NSCLC. These results are robust over

Table 4. Two-way sensitivity analyses

		ICER			
		T1 cancer		T2 cancer	
Parameter	Range studied	Lower	Upper	Lower	Upper
Probabilities					
NED to nodal recurrence	5–15%	SBRT*	SBRT†	SBRT*	SBRT*
NED to metastasis	5–25%	SBRT*	SBRT†	SBRT*	SBRT*
Recurrence to death (1-y probability)	50–100%	SBRT†	SBRT*	SBRT*	SBRT*
SBRT Grade 3 pneumonitis rate	5–20%	SBRT*	SBRT*	SBRT*	SBRT*
Pneumothorax rate	0–26%	SBRT†	SBRT*	SBRT*	SBRT*
Utility values					
NED	0.6–0.95	SBRT†	SBRT*	SBRT*	SBRT*
Recurrence	0.2–0.576	SBRT†	SBRT†	SBRT*	SBRT*
Costs					
3D-CRT	$5,000–$15,000	SBRT†	SBRT†	SBRT*	SBRT*
SBRT	$10,000–$20,000	SBRT*	RFA†	SBRT*	SBRT*
RFA	$3,000–$12,000	SBRT†	SBRT*	SBRT*	SBRT‡
Palliative care	$10,000–$50,000	RFA†	SBRT†	SBRT*	SBRT*
Non-cancer end-of-life care	$10,000–$50,000	SBRT*	SBRT†	SBRT‡	SBRT*

Abbreviations: ICER = incremental cost-effectiveness ratio; NED = no evidence of disease; SBRT = stereotactic body radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy; RFA = radiofrequency ablation.

* Scenarios in which the incremental cost-effectiveness ratio for SBRT is less than $25,000 per quality-adjusted life-year.

† Scenarios in which the incremental cost-effectiveness ratio for SBRT or RFA is between $25,000 per quality-adjusted life-year and $50,000 per quality-adjusted life-year.

‡ Scenarios in which SBRT dominates the other two strategies.

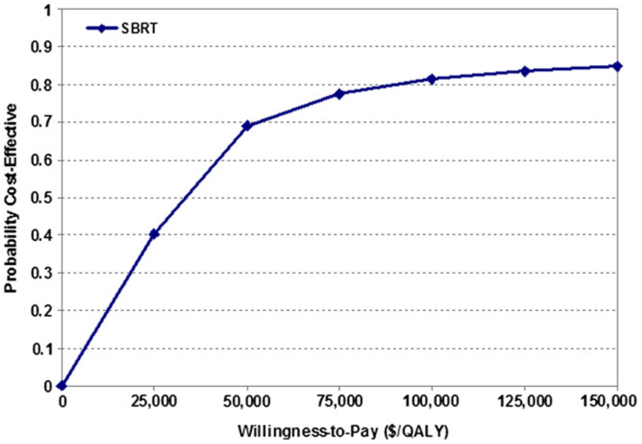

Fig. 2. Acceptability curve. This curve represents the proportion of trials drawn on a hypothetical distribution of unknown parameters that result in an incremental cost-effectiveness ratio for stereotactic body radiotherapy (SBRT) less than the societal willingness to pay. Varied parameters include efficacy of three-dimensional conformal radiation therapy (3D-CRT), SBRT, and radiofrequency ablation (RFA), as well as utility values of no evidence of disease (NED) and recurrence health states. QALY = quality-adjusted life-year.

a wide range of assumptions, including the efficacy of each treatment modality, natural history of Stage I lung cancer (*e.g.,* nodal and distant recurrence risks), health state utility values, and costs. Even when the costs of the less efficacious therapies were substantially lowered, SBRT was still clearly the most cost-effective strategy.

As shown in the one-way, two-way, and probabilistic sensitivity analyses, there were only a few parameters that substantially affected the model results. The one key variable that appeared to change the outcome was the local recurrence risk of RFA. If the 3-year local recurrence risk of RFA was 90% and the risk for SBRT remained at 88% (base-case assumption), the less expensive RFA will obviously dominate the analysis. Because tumor size is the largest determinant of failure rates, we then performed a two-way analysis comparing the three treatments with small and large tumors. This analysis was a more fair comparison, because the tumors that can be successfully treated by RFA should also be more easily ablated with radiotherapy. Indeed, for both T1 and T2 malignancies, SBRT was still the most cost-effective treatment modality over many assumptions. Furthermore, if SBRT is not available, RFA would be the most cost-effective therapy for small cancers, whereas 3D-CRT would be the preferred modality for larger lesions.

The implications of this study could affect a significant number of patients, because an estimated 25% to 35% of early-stage lung cancer patients are not medically fit for lobar resection, and thus alternative therapies must be implemented (24). Furthermore, if computed tomography–based screening becomes an accepted approach for patients at risk for lung cancer, the number of individuals with a new diagnosis of Stage I lung cancer would clearly increase (25).

Until recently, the only treatment for such inoperable patients was conventional radiation treatment, which was inconvenient and relatively ineffective. As SBRT and RFA have become more established and studied, it has become clear that they are viable options for treatment of this disease (1). However, until the present analysis, it was unknown whether the increased efficacy of SBRT justified its higher cost or whether the lower cost of RFA could overcome its variable efficacy. As we have shown, the superb control rates with SBRT overwhelm almost any increase in cost.

This study has several limitations. First, any cost-effectiveness analysis is based on key assumptions that may affect its results. In this analysis we based our clinical parameters on single-arm Phase II data and retrospective studies, because there has never been—and likely never will be—a prospective comparison of the three techniques. Our model is therefore based on the best existing data. It is important to mention that the majority of local control data for SBRT are derived from studies of T1 rather than T2 tumors, which may overstate the efficacy of the technique with larger cancers. However, we used a conservative estimate for local control in this setting (78%), which is consistent with the reported data thus far, and SBRT was still cost-effective for T2 malignancies (22).

Given the recognized parameter uncertainty in any model, sensitivity analyses significantly improve the validity of cost-effectiveness analyses by testing disease models over a wide range of assumptions and values. We tested our model over a spectrum of plausible assumptions, including varying the underlying local recurrence rates after the three treatments, natural history of Stage I lung cancer, utility values, and treatment costs, and consistently found SBRT to be cost-effective in comparison to 3D-CRT and RFA across a wide range of societal WTP levels. We therefore feel confident in our findings despite the assumptions inherent in modeling disease outcomes using limited available data.

In addition, our analysis was performed from the payer perspective (*i.e.,* Medicare) rather than a societal perspective (26). Because the vast majority of these patients are covered by Medicare, and the issues of cost-effectiveness are now central to the arguments favoring health care reform, we thought it was particularly relevant to take the payer perspective. Moreover, given the consistent findings in the sensitivity analyses and the minimal additional societal costs for these elderly patients—such as the time and productivity costs of treatment—our conclusions would hold true from any economic perspective.

Finally, it is important to note that this cost-effectiveness analysis applies only to peripheral tumors. As shown in two studies, performing SBRT for centrally based lesions, defined as within 2 cm of the proximal bronchial tree, can result in excess morbidity and mortality (27, 28). Indeed, currently, RTOG is performing a Phase I study evaluating the safety of various hypofractionation regimens. On the other hand, 3D-CRT is significantly more tolerable when treating early-stage lung cancers located in the center of the chest; thus one cannot apply our findings to medially located lesions.

In conclusion, we have shown that, based on currently available data, SBRT is the most cost-effective nonsurgical treatment for peripheral, early-stage lung cancers. Our results make a strong argument that SBRT should be the primary reimbursed therapy for these tumors in medically compromised individuals, except in those with very small peripheral lesions that may be successfully ablated by RFA. If SBRT is available, conventional fractionated radiotherapy no longer appears to be a viable treatment approach for peripheral, early-stage lung cancers, based either on efficacy or on cost outcomes. This study is the first of its kind to analyze the cost-effectiveness of SBRT; as SBRT becomes used in more clinical situations, it is imperative to assess its cost-effectiveness as well as its efficacy.

REFERENCES

1. Powell JW, Dexter E, Scalzetti EM, *et al*. Treatment advances for medically inoperable non-small-cell lung cancer: Emphasis on prospective trials. *Lancet Oncol* 2009;10:885–894.
2. Bradley JD, Wahab S, Lockett MA, *et al*. Elective nodal failures are uncommon in medically inoperable patients with Stage I non-small-cell lung carcinoma treated with limited radiotherapy fields. *Int J Radiat Oncol Biol Phys* 2003;56:342–347.
3. Sibley GS, Jamieson TA, Marks LB, *et al*. Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: The Duke experience. *Int J Radiat Oncol Biol Phys* 1998;40:149–154.
4. Chen M, Hayman JA, Ten Haken RK, *et al*. Long-term results of high-dose conformal radiotherapy for patients with medically inoperable T1-3N0 non-small-cell lung cancer: Is low incidence of regional failure due to incidental nodal irradiation? *Int J Radiat Oncol Biol Phys* 2006;64:120–126.
5. Bradley J, Graham MV, Winter K, *et al*. Toxicity and outcome results of RTOG 9311: A phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. *Int J Radiat Oncol Biol Phys* 2005;61:318–328.
6. Yuan S, Sun X, Li M, *et al*. A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III nonsmall cell lung cancer. *Am J Clin Oncol* 2007;30:239–244.
7. Fakiris AJ, McGarry RC, Yiannoutsos CT, *et al*. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: Four-year results of a prospective phase II study. *Int J Radiat Oncol Biol Phys* 2009;75:677–682.
8. Weinstein MC, Skinner JA. Comparative effectiveness and health care spending-Implications for reform. *N Engl J Med* 2010;362:460–465.
9. Sonnenberg FA, Beck JR. Markov models in medical decision making: A practical guide. *Med Decis Making* 1993;13:322–338.
10. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: A systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. *J Clin Oncol* 2008;26:4617–4625.
11. Dunlap NE, Cai J, Biedermann GB, *et al*. Chest wall volume receiving >30 Gy predicts risk of severe pain and/or rib fracture after lung stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys* 2010;76:796–801.
12. Simon CJ, Dupuy DE, DiPetrillo TA, *et al*. Pulmonary radiofrequency ablation: Long-term safety and efficacy in 153 patients. *Radiology* 2007;243:268–275.
13. Lencioni R, Crocetti L, Cioni R, *et al*. Response to radiofrequency ablation of pulmonary tumours: A prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). *Lancet Oncol* 2008;9:621–628.
14. Campbell DE, Lynn J, Louis TA, *et al*. Medicare program expenditures associated with hospice use. *Ann Intern Med* 2004;140:269–277.
15. Red book. Medical Economics; 2007. Thomson Healthcare. New York, New York.
16. A comprehensive cost analysis of Medicare Home Oxygen Therapy: A study for the American Association for Homecare. *Morrison Informatics I* 2006;20. Mechanicsburg, PA.
17. IRP Web Medicare DRG/Calculator; 2009. Available at: www.irp.com. Last accessed June 18, 2010.
18. AMA Bookstore; 2010. Available at: https://catalog.ama-assn.org/Catalog/cpt/cpt_search.jsp?_requestid=15820. Last accessed June 18, 2010.
19. Doyle S, Lloyd A, Walker M. Health state utility scores in advanced non-small cell lung cancer. *Lung Cancer* 2008;62:374–380.
20. Timmerman R. Stereotactic body radiation therapy for medically inoperable early-stage lung cancer patients: Analysis of RTOG 0236. Chicago, IL: Presented at the American Society for Radiation Oncology National Meeting; 2009.
21. Timmerman R, Paulus R, Galvin J, *et al*. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010;303:1070–1076.
22. Baumann P, Nyman J, Hoyer M, *et al*. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol* 2009;27:3290–3296.
23. Johannesson M, Pliskin JS, Weinstein MC. A note on QALYs, time tradeoff, and discounting. *Med Decis Making* 1994;14:188–193.
24. Bach PB, Cramer LD, Warren JL, *et al*. Racial differences in the treatment of early-stage lung cancer. *N Engl J Med* 1999;341:1198–1205.
25. Henschke CI, Yankelevitz DF, Libby DM, *et al*. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006;355:1763–1771.
26. Gold M, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.
27. Timmerman R, McGarry R, Yiannoutsos C, *et al*. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006;24:4833–4839.
28. Song SY, Choi W, Shin SS, *et al*. Fractionated stereotactic body radiation therapy for medically inoperable stage I lung cancer adjacent to central large bronchus. *Lung Cancer* 2009;66:89–93.