A comparison of surgical intervention and stereotactic body radiation therapy for stage I lung cancer in high-risk patients: A decision analysis

Varun Puri, MD,^a Traves D. Crabtree, MD,^a Steven Kymes, PhD,^b Martin Gregory, BS,^b Jennifer Bell, BSN,^a Jeffrey D. Bradley, MD,^c Clifford Robinson, MD,^c G. Alexander Patterson, MD,^a Daniel Kreisel, MD, PhD,^a Alexander S. Krupnick, MD,^a and Bryan F. Meyers, MD, MPH^a

Objective: We sought to compare the relative cost-effectiveness of surgical intervention and stereotactic body radiation therapy in high risk patients with clinical stage I lung cancer (non-small cell lung cancer).

Methods: We compared patients chosen for surgical intervention or SBRT for clinical stage I non-small cell lung cancer. Propensity score matching was used to adjust estimated treatment hazard ratios for the confounding effects of age, comorbidity index, and clinical stage. We assumed that Medicare-allowable charges were \$15,034 for surgical intervention and \$13,964 for stereotactic body radiation therapy. The incremental cost-effectiveness ratio was estimated as the cost per life year gained over the patient's remaining lifetime by using a decision model.

Results: Fifty-seven patients in each arm were selected by means of propensity score matching. Median survival with surgical intervention was 4.1 years, and 4-year survival was 51.4%. With stereotactic body radiation therapy, median survival was 2.9 years, and 4-year survival was 30.1%. Cause-specific survival was identical between the 2 groups, and the difference in overall survival was not statistically significant. For decision modeling, stereotactic body radiation therapy was estimated to have a mean expected survival of 2.94 years at a cost of \$14,153 and mean expected survival with surgical intervention was 3.39 years at a cost of \$17,629, for an incremental cost-effectiveness ratio of \$7753.

Conclusions: In our analysis stereotactic body radiation therapy appears to be less costly than surgical intervention in high-risk patients with early stage non-small cell lung cancer. However, surgical intervention appears to meet the standards for cost-effectiveness because of a longer expected overall survival. Should this advantage not be confirmed in other studies, the cost-effectiveness decision would be likely to change. Prospective randomized studies are necessary to strengthen confidence in these results. (*J Thorac Cardiovasc Surg* 2012;143:428-36)

Optimal treatment for patients with early-stage lung cancer with significant comorbidities remains a challenging problem. Surgical resection has been considered the gold standard for patients with acceptable risk, but patients with significant comorbidities and compromised lung function have higher morbidity and mortality after surgical intervention.¹ Stereotactic body radiation therapy (SBRT) is increasingly recognized as a favorable option in patients who are not considered operative candidates for early-stage lung cancer.²⁻⁵ Retrospective studies have compared surgical intervention and SBRT in high-risk patients,^{6,7}

but there remains equipoise among clinicians treating high-risk patients with early-stage lung cancer. This has prompted a cooperative group-sponsored prospective randomized trial comparing the 2 treatments in high-risk patients that has recently started accruing (American College of Surgeons Oncology Group Z4099/Radiation Therapy Oncology Group [RTOG] 1021).

Because resources are limited, it is reasonable to compare the costs of various treatment options for common diseases, especially if treatments lead to similar clinical outcomes. Economic evaluation is a method to examine this tradeoff between the costs and effects of comparative treatments.⁸ The effectiveness of treatments is evaluated in terms of survival (life years) attributable to the treatment or quality-adjusted life years (QALYs).

SBRT for lung cancer has been the subject of several recent cost-effectiveness analyses.⁹⁻¹¹ SBRT has been compared favorably with conventional external beam radiation therapy and radiofrequency ablation in these models, either proving dominant or providing improved effectiveness at acceptable cost. The comparison of SBRT with particle therapy (protons and carbon ions) was inconclusive in terms of cost-effectiveness.¹¹ Surgical

From the Department of Surgery,^a the Center for Economic Evaluation in Medicine,^b and the Department of Radiation Oncology,^c Washington University School of Medicine, St Louis, Mo.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Read at the 91st Annual Meeting of The American Association for Thoracic Surgery, Philadelphia, Pa, May 7-11, 2011.

Received for publication May 8, 2011; revisions received Oct 15, 2011; accepted for publication Oct 28, 2011; available ahead of print Dec 12, 2011.

Address for reprints: Varun Puri, MD, Department of Surgery, Washington University School of Medicine, 660 South Euclid Ave, Campus Box 8234, St Louis, MO 63110 (E-mail: puriv@wudosis.wustl.edu).

0022-5223/\$36.00

Copyright © 2012 by The American Association for Thoracic Surgery

doi:10.1016/j.jtcvs.2011.10.078

Abbreviations and Acronyms

ACE	= Adult Co-Morbidity Evaluation
DLCO	= carbon monoxide diffusion in the lung
FEV ₁	= forced expiratory volume in 1 second
NSCLC	= non-small cell lung cancer
PSM	= propensity score matching
QALY	= quality-adjusted life year
RTOG	= Radiation Therapy Oncology Group
SBRT	= stereotactic body radiation therapy

treatment for lung cancer has not been the subject of scrutiny in cost-effectiveness analyses. The objective of the current study was to compare the relative cost-effectiveness of surgical intervention and SBRT in high-risk patients with clinical stage I non-small cell lung cancer (NSCLC).

MATERIALS AND METHODS

We constructed a Markov decision model to describe the experience of persons undergoing surgical intervention or SBRT for clinical stage I NSCLC. Data for the efficacy of surgical intervention and SBRT were obtained through a review of medical records of patients treated with surgical intervention or SBRT for clinical stage I NSCLC staged based on the results of computed tomographic and positron emission tomographic scanning at Washington University in St Louis. All surgical patients with clinical stage I lung cancer treated between January 1, 2000, and December 31, 2006, and all patients between February 1, 2004, and May 5, 2007, with clinical stage I lung cancer undergoing treatment with SBRT were included and analyzed according to a protocol approved by our institutional review board. Comorbidity scores were recorded prospectively by using the Adult Co-Morbidity Evaluation (ACE) 27 scoring system. The ACE-27 is a unique 27-item comorbidity index developed for patients with cancer that is easy to use and has demonstrated good ability to define unique prognostic subgroups. Data on patients' demographics, history and physical examination results, evaluation by means of chest computed tomographic scans and fluorodeoxyglucose positron emission tomographic scans, operative reports, and final pathology reports (where available) were obtained from medical records. Current standard SBRT dosing at our center delivers 54 Gy in 3 fractions over 8 to 14 days, as demonstrated in trials by the RTOG. The SBRT device used was the Trilogy system (Varian Medical Systems, Inc, Palo Alto, Calif). This device does not generally require the placement of fiducial markers.

It is well known that the patients referred to SBRT and surgical intervention in a clinical setting have markedly different expected mortalities. In our multidisciplinary setting patients are typically seen by a surgeon at diagnosis, and a decision is made as to whether surgical intervention can be safely performed. The vast majority of patients undergoing SBRT had been refused resection by the surgical team. This did introduce a significant selection bias in the patient population. This selection bias might put the patients undergoing SBRT at an unmeasurable disadvantage. This made creating matched cohorts difficult. We attempted to address this using propensity scoring methods.

Propensity score matching (PSM) was performed between the surgical intervention and SBRT groups on the basis of ACE-27 scores, age (71.5 vs 71.8 years), and clinical tumor (T) stage (70% T1 vs 68% T1). Statistical analysis was performed with SPSS 11.0 software for Windows (SPSS, Inc, Chicago, Ill).⁶ In the PSM analysis logistic regression was used to estimate the corresponding scores from the baseline patient covariates. To find

matched patients from the 2 groups, we adopted a caliper matching approach. Starting with most stringent radii (0.0005 and 0.001), only a very small number of surgical patients could be matched because of the significant comorbidity of patients in the SBRT group. At a caliper radius of 0.005, 57 patients in each group could be matched.⁶

According to the recommendation of the Panel on Cost-effectiveness in Health and Medicine, we based costs on the Medicare-allowable charges.¹² Costs for patients undergoing surgical intervention were \$15,034 for those who did not undergo chemotherapy and \$24,134 for patients who underwent chemotherapy. We assumed that surgical mortality resulted in increased charges (Table 1).¹³⁻¹⁵ The Medicare-allowable charges for patients undergoing SBRT were \$13,964 for uncomplicated patients.

The Markov decision model was constructed by using TreeAge 2009 software (TreeAge Software, Williamsport, Mass) and estimated by using a microsimulation process.¹⁶ Microsimulation refers to a simulation process in which simulated participants are assigned characteristics on an individual basis and pass through the model one at a time, facing probability nodes as they pass through the model. Each time they reach the probability node, the occurrence of an event is determined by the result of a probabilistic distribution (akin to the flip of a biased 2-sided coin) to that simulated individual. Transition probabilities were parameterized as a random variable by using the mean and variance to estimate a β distribution. Survival estimates were based on Kaplan-Meier survival probabilities. Each individual completes the tree (and all cycles) before another simulated individual enters the model and the value of each transition probability is resampled. In our simulation the cohort had 1000 simulated members and was resampled 500 times (for a total of 500,000 trials). This approach allows the investigator to fully recognize the influence of both individual- and group-level variation on the study results.

The Markov model is a mathematic representation of an iterative process, with a Markov cycle representing the length of the iterative process.² In this case the iterative process describes the experience of a patient undergoing either surgical intervention or SBRT. In the surgical arm the patient initially has surgical intervention, and we assume that the operation is successful or that she or he dies. If the operation is successful, the tissue is analyzed, and if the NSCLC is stage N0, the patient then cycles through 5 years, during which there is a chance of recurrence or death from other causes (ie, the same background risk of mortality of the general public). If the cancer is upstaged to N1 or N2, the patient might receive chemotherapy. Regardless of whether chemotherapy is given, patients face an increased possibility of recurrence or death over that experienced by patients at stage N0. If the cancer is staged N2, there is an increased probability of recurrence and death over that seen in patients with stage N0 or N1 disease.

Patients undergoing SBRT follow a much simpler path. With SBRT, the patient faces the possibility of complications and consequent cost. Mortality for the simulated participants in the SBRT arm was based on that observed in the SBRT study cohort. Because there is no nodal tissue taken from patients undergoing SBRT, there is no pathological nodal staging of their disease. Therefore the mortality risk estimated for these cohort members is the average of patients who underwent SBRT. There is no parsing of mortality risk by disease severity as with the surgical group.

The influence of uncertainty on model results was evaluated in 2 ways. First, we performed 1- and 2-way sensitivity analyses to determine the effect of our parameter assumptions on the outcome. For this process, the value of each parameter was varied across the entire relevant range, and the outcome was assessed. To test the overall stability of the model, we conducted probabilistic sensitivity analysis by using the 2-stage Monte Carlo approach defined above. Cost-effectiveness acceptability graphs¹⁷ were plotted based on the net benefit estimated for each simulation. For this purpose, net benefit is calculated as follows:

$$(\text{Patient years lived} \times \text{Willingness to pay}) - \text{Cost of treatment} \\ = \text{Net benefit.}$$

TABLE 1. Costs of therapy used in the decision model

Clinical scenario/intervention	Cost (2010 dollars)	Source
Surgical intervention for early-stage lung cancer	15,034	CMS allowable
Surgical mortality	40,100	CMS allowable
SBRT (3 fractions)	13,964	CMS allowable
Pulmonary complications	11,000	CMS allowable, Reference ^{24,25}
Chemotherapy	9,100	Reference ²⁶

CMS, Center for Medicare and Medicaid Services; SBRT, stereotactic body radiation therapy.

Here, willingness to pay would be the willingness to pay for a life year gained. Because there is no known willingness to pay for a life year gained, we varied this across a wide range of values (\$0–\$200,000) to determine what influence this assumption would have on our results.

RESULTS

Of 462 patients undergoing surgical intervention and 76 undergoing SBRT, 114 patients (57 in each arm) were selected by means of propensity matching (Table 2). In the surgical group operative mortality was 4 (7%) of 57. Median survival was 4.2 years, and 4-year survival was 51.4% (n = 21). Thirteen of 53 surgical survivors with incidental N1/N2 disease (11 with N1 and 2 with N2 disease) were eligible for chemotherapy. Of these, 7 patients underwent chemotherapy. In the SBRT arm there was no treatment-related mortality, and the rate of major morbidity was 1.8% (1/57). None of the patients undergoing SBRT received chemotherapy. Median survival was 2.9 years, and 4-year survival was 30.1% (n = 12, $P = .101$). The overall and cause-specific survival for both groups was not significantly different and is depicted in Figures 1 and 2.

TABLE 2. Pretreatment and operative characteristics of surgically treated patients and patients undergoing SBRT for clinical stage I lung cancer

Variable	Surgical intervention (n = 57)	SBRT (n = 57)	P value
Mean age (y)*	71.54 ± 7.9	71.79 ± 10.6	.889
Median age (y)	73 (range, 47–90)	72 (range, 50–94)	
Male sex	34 (59.6%)	23 (40%)	.039
Clinical T1*	40 (70.2%)	39 (68.4%)	.839
FEV ₁ , % predicted (mean)	0.77	0.50	<.001
DLCO, % predicted (mean)	0.81	0.50	.01
ACE score 2–3*	36	39	.501
Operation			
Lobectomy	46 (80.7%)	NA	
Sublobar resection	11 (19.3%)	NA	

ACE, Adult Co-Morbidity Evaluation; DLCO, carbon monoxide diffusion in the lung; FEV₁, forced expiratory volume in 1 second; NA, not applicable; SBRT, stereotactic body radiation therapy. *Variables considered in propensity matching.

FIGURE 1. Kaplan-Meier plot of overall survival for the 2 groups: log rank = 2.692, $P = .10$. SBRT, Stereotactic body radiation therapy.

The results of our cost-effectiveness analysis are presented in Table 3, and the Markov diagram is depicted in Figure 3. The expected cost of treating patients with surgical intervention was \$17,629, and there was an expected survival of 3.39 years during the 5-year period evaluated in modeling. Compared with SBRT, patients treated with surgical intervention incurred an expected incremental cost of \$3476 but lived an additional 0.45 years, resulting in an incremental cost-effectiveness ratio of \$7753 per additional year of survival.

FIGURE 2. Kaplan-Meier plot of cause-specific survival for the 2 groups: log rank = 0.449, $P = .50$. SBRT, Stereotactic body radiation therapy.

TABLE 3. Results of base case cost-effectiveness analysis

Strategy	Total cost	Incremental cost	Total effectiveness (y)	Incremental effectiveness (y)	Incremental cost-effectiveness ratio (cost/y)
SBRT	\$14,153		2.94		
Surgical intervention	\$17,629	\$3476	3.39	0.45	\$7753

SBRT, Stereotactic body radiation therapy.

The results of 1-way sensitivity analysis are presented in Table 4. The cost-effectiveness decision was most sensitive to the rate of surgical mortality and N2 metastasis. For the cost-effectiveness decision to change, the rate of surgical mortality must increase by more than 2-fold from the base of 7%, and the rate of N2 metastases must increase by 4-fold from the base of 3.5%.

Finally, the result of our probabilistic sensitivity analysis is shown in the cost-effectiveness acceptability curve in Figure 4. This figure illustrates the results of our Monte Carlo simulation by summarizing the proportion of cases for each of the 500,000 simulated trials for which the indicated treatment option (surgical intervention or SBRT) resulted in the most net benefit at that willingness to pay. For instance, at a willingness to pay of \$72,000 per life year gained, approximately 85% of the trials resulted in greater net benefit for surgical intervention than SBRT. This would imply (given the assumptions of our model) that a policymaker with a willingness to pay of \$72,000 per life year gained would make the correct decision 85% of the time should she or he choose to have the patient undergo surgical intervention (where “correct” is defined as generating the most net benefit).

DISCUSSION

The majority of patients in the surgical arm underwent lobectomy. This is in contrast to some other surgical series in which authors have used sublobar resections in high-risk patients.¹⁸⁻²¹ A comparison between patients undergoing SBRT and those undergoing sublobar resection would be a more ideal cohort, but our limited number of patients undergoing sublobar resection precluded a meaningful comparison in the current series. This distribution in our series is likely related to the selection process of propensity matching, in which lung function is only one aspect of the comorbidity index. Also, the forced expiratory volume in 1 second (FEV₁) and carbon monoxide diffusion in the lung (DLCO) percentages in our surgical patients were higher than those in the patients in the aforementioned series, as well as those in the SBRT arm of the current study. Attempts at using more stringent matching criteria between the 2 groups, including lung function tests specifically, yielded very few patients for comparison. The surgical mortality in our selected high-risk surgical patients was 7%, which is higher than the 1% to 4% mortality generally reported

for lobectomy.¹ Among our low-risk surgical patients, the mortality was 2.7% (11/405). The 4-year survival in the 57 surgical patients was 51%. This is slightly lower than the survival seen in large databases (clinical stage IA, 50% 5-year survival; clinical stage IB, 43% 5-year survival)²² and is likely related to the selection of a higher-risk group for study. The clinical outcomes in the SBRT cohort were similar to published data for medically inoperable patients undergoing SBRT, both in terms of complications and survival.²⁻⁴

For the purpose of this study, we used Medicare-allowable charges as costs where possible. This approach ensures uniformity of cost data and makes the results as broadly applicable as possible and has been used by others.⁹ Medicare-allowable charges vary geographically, but generally, the direction and degree of change (increase or decrease) can be expected to be similar for both treatment arms. Alternate standardized sources of cost have been used in other studies.¹⁰⁻¹² Although it is meaningful to use a standardized system of cost estimation for economic analyses in medicine, charges billed by individual institutions for the same service vary widely,⁹ as does the eventual amount reimbursed by private insurers. There is also an understandable reluctance on the part of institutions to share their actual cost and charge information, thus explaining the lack of this information in published literature.

The cost-effectiveness analysis in the present study was performed from a payer’s perspective. The payer is defined as an individual or organization that assumes financial responsibility for health care services. Alternate approaches to economic analyses in medicine are to consider the societal perspective or a combined approach.^{23,24} The societal perspective is the broadest possible perspective for an economic evaluation. It includes all program costs, no matter who incurs them, and all program consequences, no matter who experiences them. In the societal perspective the net cost of an intervention is calculated by deducting the cost of disease averted and the cost of productivity losses from the program cost. Thus an intervention that is more effective and also more costly from a payer’s perspective is likely to look more attractive (lower incremental cost-effectiveness ratio) from a societal perspective when costs averted are deducted from the cost of the intervention.

We used absolute survival in years for the 2 treatment arms for the effectiveness data in our study. An alternate

GTS

FIGURE 3. Markov model depicting the decisions analysis showing the surgical intervention and stereotactic body radiation therapy (SBRT) arms.

approach used by several authors is to use QALYs. Any state of health or disability is assigned a utility on a scale ranging from 0 (immediate death) to 1 (a state of perfect health) to calculate QALYs. The outcome of any health

intervention can then be calculated as the product of the increase in utility that it might cause and the time in years over which it might be enjoyed. Because our study was retrospective, we could not interview patients to assign a utility value

FIGURE 4. Cost-effectiveness acceptability curve based on the results of Monte Carlo simulation. At a willingness to pay of \$72,000 per life year gained, approximately 85% of the trials resulted in greater net benefit for surgical intervention than for stereotactic body radiation therapy (SBRT).

to the absolute survival. Utilities are currently measured by using different techniques, and the results vary according to the method used.²⁵ Thus reliability cannot be assumed, especially when utilities are measured by using different techniques. This prevented us from using utilities in published literature for calculating QALYs in our patients. Additionally, because we did not use QALYs in the current study, we could not state a level of willingness to pay.

Our sensitivity analyses demonstrated that the cost-effectiveness decision was extremely robust to our model assumptions. The only parameters that affected the decision were the rate of surgical mortality and the rate of metastasis. However, metastases are a function of disease severity and in this manner affect postoperative mortality and cost of treatment through the use of chemotherapy. Increased risk of metastases shortens life expectancy for surgical patients, but because we do not know the rate of metastases in patients undergoing SBRT, we could not include this parameter in the SBRT arm of the economic model. The purpose of sensitivity analyses is to assess the influence of a change in the true population parameter on the cost-effectiveness decision. If the true rate of N2 metastases in the population was 15% (rather than 3.5%), mortality would be affected for patients undergoing SBRT, as well as patients undergoing surgical intervention. If we were to reflect this in our modeling, mortality in the SBRT arm should be changed as the N1 and N2 rate is increased in the surgical arm. However, we lacked evidence on which to base such parameters. Therefore we took the more conservative approach of affecting only the surgical arm. This makes it likely we are overstating the importance of N2 metastases in the cost-effectiveness decision.

TABLE 4. Results of 1-way sensitivity analysis

Variable (base case value)	Value tested	ICER
Surgical mortality (7%)	0%	\$2583
	17%	\$68,859
	20%	Surgery dominated/ SBRT dominant
SBRT complications (1.8%)	0%	\$8341
	20%	\$3337
Probability of chemotherapy (50% of node positive)	0%	\$7011
	100%	\$8681
N1 mets (% of total surgeries, 19%)	0%	\$5665
	30%	\$14,355
N2 mets (% of total surgeries, 3.5%)	0%	\$7154
	15%	\$62280

The base case values are shown. The values of variables tested in the model are also shown. The cost-effectiveness decision was most sensitive to the rate of surgical mortality and N2 metastasis. *ICER*, Incremental cost effectiveness ratio; *mets*, metastases; *SBRT*, stereotactic body radiation therapy.

Our study has certain limitations. The economic advantage for surgical intervention in this analysis is the result of longer survival for surgical patients in our retrospective analysis, and if survival were identical for both groups, the cost advantage of SBRT would make it the dominant therapy choice. Our cohort study suffers from the biases of any retrospective analysis, including selection bias in treatment allocation. Thus patients undergoing SBRT, despite being matched with the surgical cohort by means of PSM, had lower performance on pulmonary function tests and suffered from selection bias and thus suffered from morbidity that might not have been captured in the propensity matching. The difference in overall survival between the 2 groups was not statistically significant; however, there appeared to be a suggestive split in the curves at later time points favoring surgical patients. However, the nearly identical cause-specific survival rates between the 2 groups (Figure 2) indicate that most patients undergoing SBRT died of causes unrelated to their lung cancer, and the oncologic superiority of either treatment arm cannot be assumed. Additionally, 11% of patients undergoing SBRT received doses of less than the biological equivalent dose threshold of 100 Gy₁₀, which has been associated with inferior local control and overall survival in prior publications.^{4,26}

The surgical patients in our series were from an earlier timeframe than the patients undergoing SBRT. This partly stems from the fact that SBRT is a relatively newer introduction to the treatment of lung cancer, and to find comparable patients in the 2 groups, we had to include surgical patients from a longer time period. This also meant that all of the surgical patients had undergone a thoracotomy for resection.

The lack of preoperative surgical staging in the patients undergoing SBRT is also a limitation of this study. Treatment options were limited in these high-risk patients, and

it was often determined that surgical staging would not significantly alter the treatment plan. Moreover, modeling always involves a degree of simplification, and a model should not be faulted because available data do not meet the ideal standards of scientific evidence.

The ideal scenario for conducting cost-effectiveness analyses in medicine is when cost and utility data are collected prospectively in a randomized controlled trial. For the current comparison between SBRT and surgical intervention in the high-risk patient with lung cancer, such a trial is currently underway (American College of Surgeons Oncology Group Z4099/RTOG 1021), and a cost-effectiveness analysis is planned. Data collected from this and other, similar larger population-based studies will further clarify the relative cost-effectiveness of surgical intervention and SBRT.

References

- Kozower BD, Sheng S, O'Brien SM, et al. STS database risk models: predictors of mortality and major morbidity for lung cancer resection. *Ann Thorac Surg.* 2010;90:875-81.
- Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA.* 2010;303:1070-6.
- Lagerwaard FJ, Haasbeek CJ, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2008;70:685-92.
- Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypofXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol.* 2007;2(suppl):S94-100.
- Bradley JD, El Naqa I, Drzymala RE, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung cancer: the pattern of failure is distant. *Int J Radiat Oncol Biol Phys.* 2010;77:1146-50.
- Crabtree TD, Denlinger CE, Meyers BF, et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg.* 2010;140:377-86.
- Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. *J Clin Oncol.* 2010;28:928-35.
- Weinstein MC, Skinner JA. Comparative effectiveness and health care spending—implications for reform. *N Engl J Med.* 2010;362:460-5.
- Lanni TB Jr, Grills IS, Kestin LL, Robertson JM. Stereotactic radiotherapy reduces treatment cost while improving overall survival and local control over standard fractionated radiation therapy for medically inoperable non-small-cell lung cancer. *Am J Clin Oncol.* 2011;34:494-8.
- Sher DJ, Wee JO, Punglia RS. Cost-effectiveness analysis of stereotactic body radiotherapy and radiofrequency ablation for medically inoperable, early-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2011 [Epub ahead of print].
- Grutters JP, Pijls-Johannesma M, Ruyscher DD, et al. The cost-effectiveness of particle therapy in non-small cell lung cancer: exploring decision uncertainty and areas for future research. *Cancer Treat Rev.* 2010;36:468-76.
- Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in health and medicine. 1st ed. New York: Oxford University Press; 1996.
- Colice GL, Morley MA, Asche C, Birnbaum HG. Treatment costs of community-acquired pneumonia in an employed population. *Chest.* 2004;125:2140-5.
- Jacobs P, Marrie TJ, Calder P. Private costs of patients hospitalized with community-acquired pneumonia. *Can Respir J.* 2005;12:205-8.
- Evans WK, Will BP, Berthelot JM, Earle CC. Cost of combined modality interventions for stage III non-small-cell lung cancer. *J Clin Oncol.* 1997;15:3038-48.
- Weinstein MC. Recent developments in decision-analytic modeling for economic evaluation. *Pharmacoeconomics.* 2006;24:1043-53.
- Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Economics.* 2001;10:779-87.
- Hsie M, Morbidini-Gaffney S, Kohman LJ, et al. Definitive treatment of poor-risk patients with stage I lung cancer: a single institution experience. *J Thorac Oncol.* 2009;4:69-73.
- Martin-Ucar AE, Nakas A, Pilling JE, West KJ, Waller DA. A case-matched study of anatomical segmentectomy versus lobectomy for stage I lung cancer in high-risk patients. *Eur J Cardiothorac Surg.* 2005;27:675-9.
- Maresh B, Forrester-Wood C, Amer K, Ascione R. Value of wedge resection for lung cancer in poor cardiopulmonary status patients. *Asian Cardiovasc Thorac Ann.* 2006;14:123-7.
- Garzon JC, Ng CS, Sihoe AD, et al. Video-assisted thoracic surgery pulmonary resection for lung cancer in patients with poor lung function. *Ann Thorac Surg.* 2006;81:1996-2003.
- Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol.* 2007;2:706-14.
- McKeage K, Perry CM, Keam SJ. Darunavir: a review of its use in the management of HIV infection in adults. *Drugs.* 2009;69:477-503.
- Nuijten M, Andress DL, Marx SE, Sterz R. Chronic kidney disease Markov model comparing paricalcitol to calcitriol for secondary hyperparathyroidism: a US perspective. *Curr Med Res Opin.* 2009;25:1221-34.
- McGregor M. Cost-utility analysis: use QALYs only with great caution. *CMAJ.* 2003;168:433-4.
- Olsen JR, Robinson CG, El Naqa I, et al. Dose-response for stereotactic body radiotherapy in early-stage non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2011;81:e299-303.

Discussion

Dr Alessandro Brunelli (Ancona, Italy). Mr Chairmen, colleagues. I have no conflicts of interest to disclose.

Dr Puri, I want to congratulate you and your colleagues from St Louis for this timely and interesting contribution. As usual, your group has performed this very accurate analysis in the context of a nonrandomized observational investigation. SBRT is emerging as an effective treatment for functionally inoperable NSCLC. However, you have demonstrated with a decision model that surgical intervention remains cost-effective, even for these high-risk patients. I have 3 comments and questions, and I will ask you one at a time.

Although propensity scoring was appropriately applied in an attempt to minimize the selection bias, the 2 groups of patients did not seem quite well matched. Surgical patients were more frequently male and had higher FEV₁ and DLCO values. Also, the vast majority of surgical patients underwent lobectomy instead of minor resection. In my opinion SBRT should be best compared with minor resection instead of lobectomy. Minor resection constituted only 19% of your surgical series. Have you tried to restrict the matching analysis only to minor resections? This would probably improve your matching and probably will influence the outcome of the decision model.

Dr Puri. Dr Brunelli, that is a very appropriate comment. For PSM, just to give you a little bit of background, we had about 500 patients in the surgical arm and about 85 patients in the stereotactic radiation arm, which was used as a dataset for abstracting these 57 patients. At the very outset, we set extremely stringent criteria in terms of comorbidities and lung function tests to match these patients. We came up with about 28 or 30 patients we could actually match, therefore about 15 in each arm, which eventually led us to believe that there was no way that we could keep subsequent criteria and come up with a number of patients who could actually be analyzed.

Therefore we used the caliper matching method; I showed you a slide in which the caliper radius that was used was 0.005. Therefore in a caliper matching method, which essentially means at the

center of the circle, the patients are perfectly matched. Then you use a radius and draw a circle around that center. All the patients who fall within that circle are considered well matched by using the propensity score analysis. Therefore if you increase the radius of the caliper, a larger number of patients will be well matched by means of PSM.

When we used extremely stringent radius criteria, we again came up with about 25 or 30 patients who could be matched. Therefore we had to gradually make our criteria more lax to come up with an analyzable number of patients. Thus we do have, I would say, an unmeasurable bias against the patients undergoing SBRT, but this is the best PSM that we could achieve.

Dr Brunelli. In the construction of the propensity score, you used the adult comorbidity evaluation score. By the nature of the patients under analysis and the methodology used to calculate the overall score, the majority of the patients had an overall score of 2 or 3, making this parameter less than ideal to discriminate between high-risk and low-risk patients in this context. Have you tried to use more individual and more specific parameters, such as FEV₁, DLCO, the presence of coronary artery disease, or body mass index, along with the ACE score, to improve your propensity score construction?

Dr Puri. The ACE-27 score is a score that is collected prospectively, and as Dr Brunelli points out, it goes from mild problems (ie, level I) to moderate (ie, level II) and severe (ie, level III) comorbidity, and most of the patients had moderate or severe comorbidities that were either level II or level III. Again, when we tried to use the ACE-27 score in addition to using FEV₁, the number of patients we could come up with that could be extremely well matched was quite small and not analyzable.

Dr Brunelli. Finally, almost 21% of the patients in the surgical arm turned out to be N-node positive, and 50% of them were submitted to adjuvant chemotherapy. However, in the decision model patients undergoing SBRT were all regarded as having pathological stage 1 disease because they had no nodal biopsy. Did some of these patients undergo chemotherapy in addition to SBRT? We assume that at least an equal proportion of patients undergoing SBRT would have node-positive disease, at least equal to the surgical patients. Have you tried to repeat the analysis by adding lymph node staging and chemotherapy probability nodes in the decision models also for the SBRT group, assuming the same probability of the surgical population? Do you have any data from your center or from the literature of concurrent SBRT and chemotherapy on which to base this methodological approach?

I thank the Association for the privilege to discuss this excellent article. Thank you very much.

Dr Puri. Dr Brunelli, with regard to your last point, you are entirely correct in biologically assuming that the incidence of nodal disease would be expected to be the same in the 57 patients undergoing SBRT as in the surgical patients. None of these patients received chemotherapy up front, and therefore they were all treated with stereotactic radiation. As we accumulated more data on recurrences, either nodal, distant, or local, they were given more therapy. However, we do not have any data for up-front chemotherapy along with stereotactic radiation in our population, and I do not believe any such data have been published in the literature.

As far as using the same assumption in a decision model, one could do so, but one would not have the results of that assumption.

For example, in our surgical patients we know which patients actually had nodal disease, and we do have outcomes in those patients as having a shorter overall and cause-specific survival. However, in the SBRT population, we do not have that privilege because we do not have pathological staging, therefore we cannot really use that assumption within the decision model within the construct of the 114 patients from our own center.

Thank you.

Dr Hiran Fernando (*Boston, Mass*). That was an excellent presentation. I am glad that you put in the plug for the Z4099 study, in which I hope many people here will enroll patients.

I have a couple of questions. In your original report of your SBRT experience, you had a number of patients with no tissue diagnosis, and therefore there were clinically suspicious lung cancers that were treated. In this model that you created for your propensity analysis, was pathological confirmation of lung cancer a requirement, or did you include patients who did not have a tissue diagnosis?

Dr Puri. There were 5 or 6 patients in this population who did not have a tissue diagnosis. Of these patients, several had recurrence at some point, and therefore we eventually had a pathological diagnosis in these patients. However, of the 57 patients, only a handful did not have tissue diagnosis.

Dr Fernando. Therefore I would suggest that another factor that should be included is the need for tissue diagnosis and then model in the pneumothorax rate that you might see with that and the need for admission to the hospital that you might need for the pneumothorax rate and perhaps look at it that way.

Also, in your morbidity outcomes you described the radiation morbidity. Did you have that morbidity taken out to 3, 6, or 9 months, when you might see the effects of radiation, pneumonitis, and the effect on pulmonary function?

Dr Puri. Correct. This morbidity was calculated over a period of 9 months from the time of initial radiation. The 1 major morbidity was a significant pneumonia requiring hospitalization. There were several minor complications, none of which required hospitalization, including rib fractures and a small incidence of pleural effusions. However, none of these were treated as an inpatient and did not significantly change the cost curve in this particular analysis; therefore I did not specifically mention those minor complications.

Dr David Sugarbaker (*Boston, Mass*). I enjoyed your article very much, and I think your whole group is to be congratulated. I just have one question, and it is really always the looming concern, particularly in a retrospective trial: bias. Presumably, each one of the patients undergoing SBRT were selected for SBRT based on a variety of different factors, one of which would be the presence or absence of N2 disease. One of the indicators to me that some bias might have played a role here, which I think we just have to account for, is the higher detectable N2 disease; it was about 20%, as I saw, for the surgically resected group. Therefore I wonder whether you could comment a little bit on bias playing into your results, which is obviously something that we avoid with an intent-to-treat design.

Thank you very much. I enjoyed your article.

Dr Puri. Thank you. Bias, as Dr Sugarbaker points out, is an intrinsic part of any retrospective analysis. First, there is a selection bias both for the surgical and SBRT arms. We carefully read these

patients, and as you saw, 85% of them had undergone a lobectomy. Therefore as a group of surgeons, we had considered those patients fit enough to undergo a lobectomy. The majority of patients who were referred for stereotactic radiation had been seen by our group and had been denied a lobar resection and thus were discussed at a multidisciplinary conference and referred for stereotactic radiation. A minority of patients had chosen not to have an operation and thus underwent stereotactic radiation. All patients, with the exception of a small handful, probably about 3 or 4 patients in this 57-patient population in the SBRT group, had undergone

computed tomographic and positron emission tomographic scanning to rule out, as effectively as possible, nodal disease in these patients. Because the study patients were from the 2004–2007 era, we have become even more stringent in trying to rule out pathological nodal disease in patients being referred for nonoperative therapies. With the advent of endobronchial ultrasonography and with the rather routine use of the video mediastinoscopy and the availability of endoscopic ultrasonography, I would say in the current day and age that we have better pathological mediastinal staging than from the timeframe in which this study was conducted.