Published in final edited form as:

Cancer. 2015 July 15; 121(14): 2341–2349. doi:10.1002/cncr.29359.

The Comparative Effectiveness of Surgery and Radiosurgery for Stage I Non-Small Cell Lung Cancer

James B. Yu, MD MHS^{1,2,3}, Pamela R. Soulos, MPH^{2,4}, Laura D. Cramer, PhD², Roy H. Decker, MD PhD^{1,2,3}, Anthony W. Kim, MD^{2,3,5}, and Cary P. Gross, MD^{2,3,4,6}

¹Department of Therapeutic Radiology, Yale School of Medicine, New Haven, CT

²Cancer Outcomes, Public Policy, and Effectiveness Research (COPPER) Center, Yale School of Medicine, New Haven, CT

³Yale Cancer Center, New Haven, CT

⁴Department of Internal Medicine, Yale School of Medicine, New Haven, CT

⁵Department of Thoracic Surgery, Yale School of Medicine, New Haven, CT

⁶Robert Wood Johnson Clinical Scholars Program, Yale School of Medicine, New Haven, CT

Abstract

Background—Although surgery is the standard treatment for early stage non-small cell lung cancer (NSCLC), stereotactic body radiotherapy (SBRT) has disseminated as an alternative therapy. The comparative mortality and toxicity of these treatments for patients of different life expectancies (LE) are unknown.

Methods—Using the Surveillance, Epidemiology, and End Results–Medicare linked database, we identified patients age ≥ 67 who underwent SBRT or surgery for stage I NSCLC from 2007–2009. Matched patients were stratified into short (<5 years) and long (≥ 5 years) LE. Mortality and complication rates were compared using Poisson regression.

Findings—Overall, 367 SBRT and 711 surgery patients were matched. Acute toxicity (0–1-month) from SBRT was lower than surgery (7.9% vs. 54.9%, $p < .001$). At 24-months post-treatment, there was no difference (69.7% vs. 73.9%, $p = .31$). The incidence rate ratio (IRR) for toxicity for SBRT vs. surgery was 0.74 [95% CI 0.64–0.87].

Overall mortality was lower for SBRT than surgery at 3-months (2.2% vs. 6.1%; $p = .005$), but by 24-months, overall mortality was higher for SBRT (40.1% vs. 22.3% $p < .001$).

For patients with short LE there was no difference in lung cancer mortality (IRR 1.01 [95% CI 0.40–2.56]). However for patients with long LE, there was greater overall mortality (IRR 1.49 [95% CI 1.11–2.01]) and a trend towards greater lung cancer mortality (IRR 1.63 [95% CI 0.95–2.79]) for SBRT vs. surgery.

Conclusions—SBRT was associated with lower immediate mortality and toxicity compared to surgery. However, for patients with long LE, there appears to be a relative benefit for surgery compared to SBRT.

Introduction

The current standard of care for the treatment of early stage non-small cell lung cancer (NSCLC) is surgery. For patients who cannot undergo surgery, several single arm prospective trials have suggested that stereotactic body radiotherapy (SBRT) is a safe and effective alternative.^{1–5} SBRT is a non-invasive treatment that delivers precisely targeted ablative doses of radiation using principles of stereotaxis, rigorous patient immobilization and/or tumor tracking, and modern radiotherapy treatment planning. Outcomes from SBRT are so promising that some investigators are beginning to advocate its use even in patients eligible for surgery⁶, though this remains controversial. However, despite the increasing adoption of SBRT, its comparative effectiveness compared to surgery remains unknown.

The difference between SBRT and surgery may be amplified for elderly patients with shorter life expectancy, who may not tolerate surgery well, and for whom immediate complications and morbidity may weigh more heavily than potential benefits in long term efficacy. For example, side effects from surgery are typically immediate, with gradual recovery. Conversely, acute toxicity from SBRT is thought to be mild, although longer-term post-radiation toxicity can develop months or years after treatment. Defining the time period within which mortality and complication differences occur is important, as after a certain amount of time, the higher “up-front” risk associated with surgery will begin to compare favorably to the potentially greater longer-term risks of SBRT. Furthermore, the difference between short and longer term toxicity and mortality may be accentuated for patients with short and longer estimates of life expectancy.

Comparing the effectiveness of SBRT and surgery is difficult. Randomized trials have either failed to accrue⁷⁸ or are many years from completion⁹. In the absence of clinical trial data, a recent retrospective analysis was performed using the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database.¹⁰ The authors found no difference in survival between patients who underwent SBRT versus surgery. However, this analysis balanced the SBRT and surgery cohorts with respect to whether patients underwent surgical staging (among other factors). This resulted in a comparison of patients who were largely pathologically unstaged. In practice, the vast majority of patients capable of undergoing surgical resection will have their lymph nodes surgically examined. Therefore, the results of this analysis—while potentially reflective of the true efficacy of surgery compared to SBRT—may not be generalizable to elderly patients undergoing these treatments in actual clinical practice and may not accurately represent the past effectiveness of SBRT and surgery.¹⁰ Furthermore, complications and the impact of life expectancy were not examined.

Therefore, we sought to address the practical knowledge gap concerning treatment outcomes among an elderly cohort of early stage NSCLC patients with differing life expectancies. Using the SEER-Medicare linked database, we investigated the comparative effectiveness of

surgery vs. SBRT by measuring complications, overall mortality and cancer specific mortality over different time periods following treatment in patients matched by comorbidity and disability.

Methods

Data source and sample selection

We used the SEER-Medicare linked database to carry out a retrospective cohort study. The SEER program publishes cancer incidence and survival information for 28% of the US population. This data is linked to Medicare claims and provides a detailed source of information of patients with cancer. The Yale Human Investigations Committee determined that this study was exempt from review.

Using patients in SEER-Medicare diagnosed from 2007–2009, we identified a sample of patients aged ≥ 67 who received either SBRT or surgery (lobar or sublobar resection) for stage I NSCLC in the 6 months following diagnosis. Treatment date was assigned as the date of first SBRT treatment or date of surgery. We included only those patients who were enrolled in the Medicare fee-for-service plan during the study period.

Construction of variables

Healthcare Common Procedure Coding System (HCPCS) codes were used to identify receipt of treatment (Appendix 1). Patient characteristics included age, sex, race, year of treatment, marital status, residence in a metropolitan county, regional median household income, and SBRT availability (as measured by intensity of SBRT use in the patient's hospital referral region of residence). Because a PET scan is suggested to improve the precision of staging, we recorded whether a PET scan had been performed in the 6 months prior to treatment. Access to primary care may influence the development or reporting of toxicity, so we recorded the receipt of an influenza vaccination or a visit to a primary care provider in the 2 years prior to diagnosis.

Comorbidity index and Life Expectancy—We used International Classification of Diseases, 9th revision (ICD-9) diagnosis codes on claims reported in the 24 months prior to diagnosis to identify a modified list of comorbidity categories described by Elixhauser et al.¹¹ (Appendix 2). Diagnosis codes had to appear on at least one inpatient claim or 2 outpatient/physician claims billed >30 days apart to be counted. We then calculated life expectancy by using a standard life table approach. Annual mortality rates were derived from a sample of non-cancer patients according to sex, age, and comorbidity. We then stratified patients by short (<5 years) or long (≥ 5 years) life expectancy.

Disability index—To provide a measure of patient functional status and ability to tolerate aggressive therapy, we used a validated disability index¹². The disability index is based on procedure codes from Medicare Part A and B claims from the 12 months prior to cancer diagnosis. We divided the index score into quartiles based on the distribution in the full study sample, with quartile 1 indicating the lowest probability of disability (Appendix 3).

Complications—Our multidisciplinary team first identified over 400 procedure and diagnosis codes that were potentially indicative of an SBRT or surgery related complication, based on clinical knowledge and literature review^{13–15}. This list of codes was reduced to those which occurred at least once in a preliminary sample of patients with stage III NSCLC who underwent extensive surgery or radiotherapy (data not shown; Appendix 1). These codes were then *a priori* categorized into 6 categories: 1) pneumonia, 2) infection, empyema, abscess, or wound complication, 3) respiratory complication, 4) cardiovascular complication, 5) esophageal complication, and 6) radiation-specific complication (i.e. claims which specifically mentioned radiation). Pneumonia was a distinct category from an empyema, abscess, or wound complication as it was felt that pneumonia that developed after treatment could potentially be due to underlying comorbidity rather than type of treatment chosen. Since certain claims indicative of respiratory complications occurred so frequently as to be non-specific, only those claims that were strongly associated with mortality were included.

Statistical analysis

Because patients who receive surgery are likely to be systematically different from patients who receive SBRT, we used propensity score matching to account for treatment selection bias. We used logistic regression, in which the outcome was receipt of SBRT versus surgery, to determine each patient's adjusted probability of receiving SBRT. We then used nearest neighbor matching without replacement to match each SBRT patient to 2 surgery patients. We were able to successfully match 96% of SBRT patients and evaluated the fit of the match using standardized differences.

For analysis of complications, patients contributed person-time until the earliest of the following events: first complication, death, loss of fee-for-service coverage, or December 31, 2010. For the analysis of overall mortality, patients contributed person-time until the earliest of death or December 31, 2010. For analysis of lung cancer-specific mortality, patients contributed person-time until the earliest of death or December 31, 2009, which was the latest date for which SEER provides cause of death. We compared the frequency of complications at different time intervals (1, 3, 6, 12, and 24 months) after treatment using the chi-squared test. Since the Cox proportional hazards assumption was violated (there was a greater proportional hazard for death and complications for surgery immediately post-treatment, and a lesser hazard as time from treatment increased), the overall incidence rate of complications and overall and lung cancer-specific survival was compared using Poisson regression with an offset for person-time. These analyses were performed for the overall matched sample, as well as for matched patients with short (<5 years) and long (≥ 5 years) life expectancies.

Results

We identified 3,852 patients who received surgery and 383 patients who received SBRT (Table 1). The proportion of patients undergoing SBRT rose from 4.4% in 2007 to 12.7% in 2009. SBRT patients were older and more likely to be female, black, and unmarried compared to surgery patients ($p<.001$ for all comparisons). Regional characteristics and

primary care access was similar between treatment groups. Patients who underwent SBRT were more likely to have received a PET scan (91.6% vs. 82.9%, $p<.001$). The SBRT treatment group also had higher disability scores (33.4% were in the highest quartile, vs. 24.1% for surgery, $p<.001$), and higher comorbidity scores (42.8% had 3 comorbidities, vs. 25.3% for surgery, $p<.001$). SBRT and surgery patients were successfully matched using propensity scores, with previously unbalanced covariates becoming balanced (Table 1). Seven hundred and eleven (711) surgery patients were matched to 367 SBRT patients. A 2:1 match was attempted for each SBRT patient but was not possible in all cases.

Complications

Patients who received SBRT were less likely to experience any complications compared to matched patients who received surgery across the 24 months of follow-up (Table 2). The lower complication rates for SBRT were due to fewer respiratory complications and infections, as well as cardiovascular complications and pneumonias from 0–1, 0–3, and 0–6 months after treatment.

Complications from surgery tended to occur in the immediate post-treatment period. For example, 54.9% of surgery patients experienced a complication within 1 month of treatment, compared to only 7.9% of SBRT patients ($p<.001$). However, in later periods of follow up, the number of patients who had a complication from SBRT rose steadily. By 24 months post-treatment, 73.9% of surgery versus 69.7% of SBRT patients experienced a complication, a difference that was no longer statistically significant. Therefore, the absolute difference in complications decreased from 48% within 0–1 month after treatment to 4% within 0–24 months after treatment.

Overall, there were 647.5 complications per 1,000 person-years for SBRT compared to 1025.4 for surgery (incidence rate ratio (IRR) 0.74 [95% confidence interval (CI) 0.64–0.87]) (Table 3). Patients with short and long life expectancy had similarly reduced incidence rate ratios of complications for SBRT compared to surgery (IRR 0.72 [95% CI 0.48–1.07] for short life expectancy, and IRR 0.76 [95% CI 0.61–0.94] for long), though only the IRR for long life expectancy patients was statistically significant.

Mortality

In the matched cohort, 3-month mortality was significantly lower for SBRT vs. surgery (2.2% vs. 6.1%; $p=.005$; Figure 1). However, at 24 months mortality was significantly higher for SBRT (40.1% vs. 22.3%; $p<.001$). Though the greater overall mortality at 24 months for SBRT vs. surgery was due in part to both cancer and non-cancer mortality, only non-cancer mortality was significantly different, indicating that non-cancer mortality may play a greater role in differences in overall mortality between SBRT and surgery. As a result, though Poisson regression revealed that the frequency of overall mortality after SBRT was significantly greater than surgery (IRR 1.61 [1.29–2.01]), lung cancer mortality was not significantly greater for SBRT (IRR 1.45 [95% CI 0.97–2.16]) compared to surgery (Table 3).

When examining complications and mortality simultaneously, early complications and death occurred for surgery, but differences decreased over time (Figure 2). For example, from 0–1

month, 54.9% of surgery patients had experienced a complication or death vs. only 8.5% of SBRT patients. However, when examining the entire 24 month period, 72.5% of surgery patients vs. 68.0% of SBRT patients had experienced complication or death.

The differences in complication and mortality rates for SBRT vs. surgery appeared similar between short and long life expectancy strata (Table 3). However, for patients with long life expectancy, the overall mortality IRR favored surgery and was statistically significant (IRR 1.49 [1.11–2.01]) for SBRT vs. surgery, in part due to the larger sample size and greater lung cancer mortality (IRR 1.63 [0.95–2.79]). For patients with short life expectancy, lung cancer mortality was equivalent between surgery and SBRT (IRR 1.01 [0.40–2.56]).

Discussion

Patients who underwent SBRT had a significantly lower rate of complications and early mortality than those who underwent surgery for stage I NSCLC. In particular, patients who underwent surgery had higher rates of infections and respiratory complications compared to those who underwent SBRT. However, over time, differences in complications and mortality decreased so that by two years after treatment, patients who underwent surgery tended to have superior outcomes in terms of overall mortality. As a result, for patients with short life expectancy, SBRT may be preferable. However, for patients with greater than 5 years of life expectancy, there appears to be a relative benefit in terms of overall and cancer specific mortality in favor of surgery over SBRT.

Our study findings are significant for several reasons. First, our analysis supports current practice patterns: the use of SBRT in patients with short life expectancy due to age or comorbidity, who are less likely to tolerate treatment related complications, as well as the use of surgery in patients who are fit and have longer life expectancy. Second, our study illustrates the importance of longitudinal analysis of patient outcomes, and the potential limitations of studies that rely on a single time point for comparison. As surgery and SBRT are inherently different treatments, it is not surprising that the time it takes to develop complications and the pattern of mortality are also different. Therefore, if one were to compare surgery and SBRT using an early time point (such as 6 month mortality), SBRT would clearly be improved in comparison to surgery. This insight is critical to the interpretation of future clinical trials comparing SBRT and surgery.

The finding of significantly increased immediate toxicity and peri-treatment mortality for surgery is consistent with other studies.^{16,17} Others have found high rates of pulmonary and cardiovascular complications after surgery¹⁷ as well as significant rates of operative mortality, in particular for patients with high operative risk, whereas treatment-related complications and deaths associated with SBRT are rare or nonexistent.¹⁶ We also found that over time, the difference in toxicity between surgery and SBRT decreased.

Not only did we find that the timing of toxicity and mortality are different for SBRT and surgery, but the relative effectiveness of these treatments varied by life expectancy. We found that overall mortality was significantly worse for patients with long life expectancy who undergo SBRT (compared to surgery) but that this difference was not significant for

those with short life expectancy. Furthermore, lung cancer mortality was worse for SBRT compared to surgery only in those patients with long life expectancy, whereas it was equivalent for those with short life expectancy. These findings highlight the importance of patient life expectancy on the relative impact of treatment, and can inform the interpretation of future comparisons of SBRT and surgery. For example, if clinical trials demonstrate improved survival with surgery, it may be due in part to the inclusion of healthier patients with longer life expectancy.

Our study is limited by factors inherent to observational claims based analyses. First, grading of toxicity was not possible. Though the toxicities that we detected were those that required intervention or merited a medical diagnosis, we did not detect milder toxicities that did not rise to medical attention and were unable to account for important subjective outcomes such as discomfort or quality of life¹⁸. Second, there may be unmeasured confounders such as comorbid illness or functional status for which we were unable to adjust¹⁹. Third, we lacked information regarding the actual dose of radiotherapy and fields used. Fourth, it is unclear whether 24 months is sufficient to capture all toxicities from treatment. Fifth, though we grouped both lobectomy and sub-lobar resection together for a general comparison of SBRT and surgery, these are in fact distinct surgeries with potentially different rates of complications. However, it appears that the number of non-anatomic (non-lobectomy) resections has been increasing since 2000.²⁰ Furthermore, there is some evidence that there is no discernable difference in survival for small tumors in the modern era between sublobar and lobar resections^{21–23} despite inferior local control²³. Finally, not all surgery was performed by thoracic surgeons. Lung resections performed by general surgeons are associated with statistically worse morbidity and mortality compared to those performed by board certified thoracic surgeons²⁴.

A final potential limitation of our study lies in the difference between pathological staging and clinical staging. SEER does not distinguish between pathologic and clinical staging and uses all available information to designate staging. As patients who underwent surgery were pathologically staged, any patients with metastatic disease found at time of surgery would be eliminated from our analysis, whereas patients in the SBRT group with occult metastatic disease may have been included. Therefore, our overall estimation of survival may be biased in favor of surgery²⁵ and the increased risk of mortality associated with SBRT may actually be less than we have estimated. Although we could have minimized this bias by matching on lymph node staging, this would have produced a cohort that was largely unstaged, as most patients who undergo SBRT do not have pathologic examination of their lymph nodes¹⁰. This would have required us to exclude the majority of surgery patients, most of whom receive pathologic lymph node examination, resulting in an analysis that may not be generalizable to the greater Medicare population. Therefore, we attempted to account for potential differences in staging by including clinical PET staging as a covariate, although we recognize that this likely did not account for all upstaging, as pathological upstaging can occur even in patients who have undergone a PET scan.

Ideally, randomized trials will eventually provide the necessary information to prove the efficacy of one treatment over the other. However, randomized trials necessarily use specifically defined temporal endpoints and investigate relatively healthy and uniform

populations treated at major academic centers. Our study, investigating elderly patients across all comorbidity and life expectancy strata, is important for those patients who may not be eligible for randomization.

Despite our analysis of patients with less than or greater than 5 years of life expectancy, It is very difficult to define the life expectancy where the relative risk and benefit changes from SBRT to surgery as this likely varies from patient to patient. For the clinician reading this study attempting to counsel patients, our study provides further impetus for frank discussion and individualized decision making, taking into account a patient's life expectancy, desire for long term cure, and appetite for treatment related complications. For researchers looking to design studies with endpoints of mortality and morbidity, our study pushes them to stratify patients by life expectancy, and examine complications and mortality for at least 2 years after treatment. In conclusion, elderly patients who undergo SBRT have fewer early complications and less early mortality compared to patients who undergo surgery. However, as time goes on, the difference in complications is reduced, and patients who undergo surgery have lower 2-year overall mortality than those who undergo SBRT, largely due to differences in non-cancer mortality. When examining patients with short and long life expectancy separately, lung cancer mortality was equivalent between SBRT and surgery for those patients with short life expectancy, and greater for SBRT in patients with long life expectancy. These findings support current practice and can inform interpretation of future studies comparing these two very different treatments.

Acknowledgements

The collection of the California cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract N01-PC-35136 awarded to the Northern California Cancer Center, contract N01-PC-35139 awarded to the University of Southern California, and contract N02-PC-15105 awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement #U55/CCR921930-02 awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California, Department of Public Health the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred. The authors acknowledge the efforts of the Applied Research Program, NCI; the Office of Research, Development and Information, CMS; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database. The interpretation and reporting of the SEER-Medicare data are the sole responsibility of the authors.

Conflicts of interest:

Drs Yu and Gross and Ms. Soulos receive research funding from 21st Century Oncology LLC. Dr. Gross has also received funding from Medtronic and Johnson & Johnson to assist with developing and implementing an approach for sharing clinical trial data.

Funding:

This work was supported by the National Cancer Institute, National Institutes of Health (R01CA149045). Dr. Yu was also supported for this work by CTSA grant KL2 RR024138 from the National Center for Advancing Translational Science (NCATS), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research.

The study sponsor (NIH) did not play a role in the design of the study; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Appendix 1: Procedure codes used to identify treatment and complications

	Healthcare Common Procedure Coding System	International Classification of Diseases, 9 th revision – Procedure	International Classification of Diseases, 9 th revision – Diagnosis
Treatment modality			
Stereotactic body radiotherapy	G0173, G0242, G0243, G0251, G0338, G0339, G0340, 0082T, 0083T, 77373, 77435		
Surgery	32442, 32500, 32657, 32480, 32482, 32484, 32486, 32503, 32663, 32520, 32522, 32525, 32657, 32500	32.20, 32.29, 32.3x, 32.4x, 32.5x	
Complication category	Healthcare Common Procedure Coding System	International Classification of Diseases, 9 th revision – Procedure	International Classification of Diseases, 9 th revision – Diagnosis
Pneumonia			486, 482.x, 480, 485, 507.0, 481, 483.x, 511.1, 484.x, 514
Abscess or wound complication	11040, 11000, 32810, 11041, 11042, 13160, 32815, 12021	86.22, 34.79, 34.03, 34.73	998.83, 998.1x, 513.0, 707.02, 513.1, 998.3x, 707.8, 998.6, 510.0
Respiratory complication (non-infectious or non-specific)		34.04, 34.09	786.3, 518.81, 518.82, 518.5, 518.4, 799.1
Cardiovascular complication	33030, 33010, 33025	37.0	410.x, 411.x, 435.x, 785.5x, 427.5, 997.02, 423.3
Esophageal	43249, 43250, 43219, 43226, 43248, 43220		530.3
Radiation-Specific			508.0, 508.1, 990

Appendix 2: Elixhauser comorbid conditions

Congestive Heart Failure
Cardiac Arrhythmia
Valvular Disease
Pulmonary Circulation Disorders
Peripheral Vascular Disorders
Paralysis
Other Neurological Disorders
Chronic Pulmonary Disease
Diabetes Uncomplicated
Diabetes Complicated
Renal Failure
Liver Disease
AIDS/HIV

Lymphoma
Rheumatoid Arthritis/collagen
Coagulopathy
Weight Loss
Fluid and Electrolyte Disorders
Deficiency Anemia
Alcohol Abuse
Drug Abuse
Psychoses
Depression

Appendix 3: Disability claims indicative of poor (+) and favorable (–) disability status

Adapted from Davidof AJ, Zuckerman IH, Pandya, et al. A novel approach to improve health status measurement in observational claims-based studies of cancer treatment and outcomes. *Journal of Geriatric Oncology*. 4:157–65, 2013.

Covariate	Poor or favorable disability
Evaluation and management (E&M)/other visits by provider specialty or site of care	
Nursing home visit	+
Dermatology E&M Visit	–
Neurology E&M Visit	+
Rheumatology E&M Visit	+
Chiropractic	–
Home Visit	+
Hospice visit	+
Minor skin procedures	+
Ambulatory musculoskeletal procedures	–
Screenings	–
Immunizations/Vaccinations	–
Major orthopedic procedures – other	+
Durable Medical Equipment	
Bath and toilet aids	–
Wheelchairs	+
Hospital bed	+
Enteral and parenteral	+
Medical/surgical supplies	+
Other	+

Covariate	Poor or favorable disability
Standard imaging – nuclear medicine	–
Other	
Ambulance	+
Electrocardiography monitoring & cardiovascular stress tests	–
Endoscopy – upper gastrointestinal	+
Endoscopy – sigmoidoscopy, colonoscopy	–
Medicaid enrollment	+
Count of E&M Visits	

References

1. Baumann P, Nyman J, Hoyer M, et al. Stereotactic body radiotherapy for medically inoperable patients with stage I non-small cell lung cancer - a first report of toxicity related to COPD/CVD in a non-randomized prospective phase II study. *Radiother Oncol.* 2008; 88:359–367. [PubMed: 18768228]
2. Lagerwaard FJ, Haasbeek CJ, Smit EF, et al. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2008; 70:685–692. [PubMed: 18164849]
3. McGarry RC, Papiez L, Williams M, et al. Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: phase I study. *Int J Radiat Oncol Biol Phys.* 2005; 63:1010–1015. [PubMed: 16115740]
4. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA.* 2010; 303:1070–1076. [PubMed: 20233825]
5. Padda SK, Burt BM, Trakul N, et al. Early-stage non-small cell lung cancer: surgery, stereotactic radiosurgery, and individualized adjuvant therapy. *Semin Oncol.* 2014; 41:40–56. [PubMed: 24565580]
6. Lagerwaard FJ, Versteegen NE, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2012; 83:348–353. [PubMed: 22104360]
7. Randomized Study to Compare Cyberknife to Surgical Resection in Stage I Non-Small Cell Lung Cancer (STARS). 2014
8. Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage (IA). Lung Cancer (ROSEL). 2014
9. Crabtree T, Puri V, Timmerman R, et al. Treatment of stage I lung cancer in high-risk and inoperable patients: comparison of prospective clinical trials using stereotactic body radiotherapy (RTOG 0236), sublobar resection (ACOSOG Z4032), and radiofrequency ablation (ACOSOG Z4033). *J Thorac Cardiovasc Surg.* 2013; 145:692–699. [PubMed: 23174176]
10. Shirvani SM, Jiang J, Chang JY, et al. Lobectomy, Sublobar Resection, and Stereotactic Ablative Radiotherapy for Early-Stage Non-Small Cell Lung Cancers in the Elderly. *JAMA Surg.* 2014
11. Elixhauser A, Steiner C, Harris DR, et al. Comorbidity measures for use with administrative data. *Med Care.* 1998; 36:8–27. [PubMed: 9431328]
12. Davidoff AJ, Zuckerman IH, Pandya N, et al. A novel approach to improve health status measurement in observational claims-based studies of cancer treatment and outcomes. *J Geriatr Oncol.* 2013; 4:157–165. [PubMed: 23795223]
13. Rueth NM, Parsons HM, Habermann EB, et al. The long-term impact of surgical complications after resection of stage I nonsmall cell lung cancer: a population-based survival analysis. *Ann Surg.* 2011; 254:368–374. [PubMed: 21617585]

14. Shapiro M, Mhango G, Kates M, et al. Extent of lymph node resection does not increase perioperative morbidity and mortality after surgery for stage I lung cancer in the elderly. *Eur J Surg Oncol.* 2012; 38:516–522. [PubMed: 22244908]
15. Shirvani SM, Klopp AH, Likhacheva A, et al. Intensity modulated radiation therapy for definitive treatment of paraortic relapse in patients with endometrial cancer. *Pract Radiat Oncol.* 2013; 3:e21–e28. [PubMed: 24674269]
16. 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; 140:377–386. [PubMed: 20400121]
17. Rueth NM, Parsons HM, Habermann EB, et al. Surgical treatment of lung cancer: predicting postoperative morbidity in the elderly population. *J Thorac Cardiovasc Surg.* 2012; 143:1314–1323. [PubMed: 22341420]
18. Moye J, June A, Martin LA, et al. Pain is prevalent and persisting in cancer survivors: differential factors across age groups. *J Geriatr Oncol.* 2014; 5:190–196. [PubMed: 24495701]
19. Shayne M, Culakova E, Poniewierski MS, et al. Risk factors for in-hospital mortality and prolonged length of stay in older patients with solid tumor malignancies. *J Geriatr Oncol.* 2013; 4:310–318. [PubMed: 24472473]
20. Kim AW, Detterbeck FC, Boffa DJ, et al. Characteristics associated with the use of nonanatomic resections among Medicare patients undergoing resections of early-stage lung cancer. *Ann Thorac Surg.* 2012; 94:895–901. [PubMed: 22835558]
21. Yendamuri S, Sharma R, Demmy M, et al. Temporal trends in outcomes following sublobar and lobar resections for small (≤ 2 cm) non-small cell lung cancers--a Surveillance Epidemiology End Results database analysis. *J Surg Res.* 2013; 183:27–32. [PubMed: 23260233]
22. Kilic A, Schuchert MJ, Pettiford BL, et al. Anatomic segmentectomy for stage I non-small cell lung cancer in the elderly. *Ann Thorac Surg.* 2009; 87:1662–1666. discussion 1667–8. [PubMed: 19463574]
23. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg.* 1995; 60:615–622. discussion 622–3. [PubMed: 7677489]
24. Schipper PH, Diggs BS, Ungerleider RM, et al. The influence of surgeon specialty on outcomes in general thoracic surgery: a national sample 1996 to 2005. *Ann Thorac Surg.* 2009; 88:1566–1572. discussion 1572–3. [PubMed: 19853114]
25. Mountain CF. Staging classification of lung cancer. A critical evaluation. *Clin Chest Med.* 2002; 23:103–121. [PubMed: 11901906]

Figure 1.

Overall and cancer-specific mortality for patients undergoing surgery or stereotactic body radiotherapy.

*Statistically significant difference in overall mortality for stereotactic body radiotherapy versus surgery.

Note: Diagonal shading represents estimated percent mortality due to the Centers for Medicare and Medicaid Services prohibition against reporting patient group sizes of fewer than 11 patients. Percent mortality displayed represents the minimum reportable value, of which actual percent mortality is less.

SBRT = Stereotactic Body Radiotherapy

Figure 2.
Percent of stereotactic body radiotherapy patients versus surgery patients experiencing any complication or death by time period.
SBRT=stereotactic body radiotherapy

Table 1

Patient sample

	Unmatched Cohort						Matched Cohort					
	SBRT	Surgery	P- value	N	%		SBRT	Surgery	P- value	N	%	
Overall	383	3852					367	711				
Patient Characteristics												
Age			<.001									0.61
66–69	43	11.2		673	17.5		42	11.4		90	12.7	
70–74	76	19.8		1237	32.1		76	20.7		162	22.8	
75–79	100	26.1		1126	29.2		98	26.7		202	28.4	
80–84	99	25.9		617	16		97	26.4		161	22.6	
85–94	65	17.0		199	5.2		54	14.7		8896	13.5	
Sex			<.001									0.77
Male	135	35.3		1761	45.7		134	36.5		266	37.4	
Female	248	64.8		2091	54.3		233	63.5		445	62.6	
Race			<.001									0.59
White	>342	>89.3		3476	90.2		>328	>89.4		634	90.2	
Black	>28	>7.3		186	4.8		>26	>7.1		56	7.8	
Other	<11**	<2.9		190	4.9		<11**	<3.0		21	3.0	
Marital status			<.001									0.95
Married	159	41.5		2200	57.1		156	42.5		302	42.5	
Unmarried	211	55.1		1540	40		198	54		381	53.6	
Unknown	13	3.4		112	2.9		13	3.5		28	3.9	
Year of diagnosis			<.001									0.69
2007	63	16.5		1365	35.4		63	17.2		133	18.7	
2008	140	36.6		1250	32.5		134	36.5		267	37.6	
2009	180	47		1237	32.1		170	46.3		311	43.7	
Regional characteristics												

	Unmatched Cohort						Matched Cohort						P-value*
	SBRT	N	%	Surgery	N	%	SBRT	N	%	Surgery	N	%	
Residence in non-metro county													0.37
No	313	81.7	3154	81.9	300	81.7	565	79.5					
Yes	70	18.3	698	18.1	67	18.3	146	20.5					
Median household income													1.00
Q1	98	25.6	814	21.1	96	26.2	192	27.0					
Q2	49	12.8	579	15	48	13.1	91	12.8					
Q3	85	22.2	791	20.5	83	22.6	161	22.6					
Q4	74	19.3	729	18.9	67	18.3	127	17.9					
Q5	77	20.1	939	24.4	73	19.9	140	19.7					
SRS availability													0.40
Not available	0	0	451	11.7	0	0	<11**	<1.6					
Moderately available	>207	>54.0	2863	74.3	>205	>55.9	431	60.6					
Highly available	>163	>42.6	504	13.1	>149	>40.6	>257	>36.1					
Unknown	<11**	<2.9	34	0.9	<11**	<3.0	<11**	<1.6					
Clinical characteristics													
PET performed													0.94
No	32	8.4	660	17.1	32	8.7	61	8.6					
Yes	351	91.6	3192	82.9	335	91.3	650	91.4					
Comorbidity													0.69
0	44	11.5	1147	29.8	43	11.7	78	11.0					
1-2	175	45.7	1731	44.9	169	46.1	347	48.8					
3	164	42.8	974	25.3	155	42.2	286	40.2					
Disability quartile													0.76
Q1	70	18.3	998	25.7	70	19.1	155	21.8					
Q2	80	20.9	979	25.4	78	21.3	148	20.8					
Q3	105	27.4	957	24.8	99	27.0	189	26.6					

		Unmatched Cohort				Matched Cohort			
		SBRT		Surgery		P-value*			
		N	%	N	%	N	%	N	%
Q4		128	33.4	928	24.1	120	32.7	219	30.8

* P values determined by chi-squared test

** CMS prohibits reporting patient groups of less than 11 patients

SBRT=stereotactic body radiotherapy

Table 2
Cumulative percent incidence of complications for the surgery and stereotactic body radiotherapy matched cohort

	0–1 month			0–3 months			0–6 months			0–12 months			0–24 months*		
	SBRT (%)	Surgery (%)	P value	SBRT (%)	Surgery (%)	P value	SBRT (%)	Surgery (%)	P value	SBRT (%)	Surgery (%)	P value	SBRT (%)	Surgery (%)	P value
Pneumonia	4.1	30.2	<.001	12.0	34.6	<.001	24.3	38.4	<.001	39.8	42.2	.45	50.3	48.9	.77
Infection, empyema, abscess, or wound complication	<3.0**	9.1	<.001	<3.0**	10.6	<.001	4.1	11.8	<.001	6.3	12.9	<.001	7.9	15.8	.01
Respiratory complication	3.5	37.1	<.001	6.5	40.1	<.001	11.7	42.3	<.001	21.3	44.3	<.001	37.6	47.3	.04
Cardiovascular	<3.0**	9.1	<.001	3.5	11.7	<.001	8.5	14.5	.004	14.7	19.1	.07	21.2	27.2	.14
RT related	<3.0**	0.0	.16	<3.0**	0	.002	4.4	<1.6**	<.001	7.1	<1.6**	<.001	7.9	0.5	<.001
Any complication	7.9	54.9	<.001	20.2	58.8	<.001	37.3	63.3	<.001	53.7	67.5	<.001	69.7	73.9	.31

* Restricted to patients who started treatment prior to 2009 and had continuous fee-for-service enrollment for 24 months after start of treatment (or until death)

** The Centers for Medicare and Medicaid Services prohibits reporting cell sizes of fewer than 11 patients

Note: Esophageal complications are not shown here because of the uniformly small frequency of complications and were not significantly different at any time point. Esophageal complications are included in tabulation of "Any complication".

SBRT=stereotactic body radiotherapy

Incidence rate and incidence rate ratios for complications, lung cancer mortality, and overall mortality for all life expectancies, as well as short and long life expectancy

Table 3

Outcome	All life expectancies		Short life expectancy (<5 years; N=131)		Long life expectancy (≥ 5 years; N=608)	
	Incidence rate (per 1,000 person-years)	Incidence rate ratio (95% CI)	Incidence rate (per 1,000 person-years)	Incidence rate ratio (95% CI)	Incidence rate (per 1,000 person-years)	Incidence rate ratio (95% CI)
Complications						
Surgery	1025.4	1.00	1804.5	1.00	903.5	1.00
SBRT	647.5	0.74 (0.64–0.87)	970	0.72 (0.48–1.07)	591.9	0.76 (0.61–0.94)
Overall mortality						
Surgery	142.6	1.00	209.8	1.00	138.4	1.00
SBRT	242.1	1.61 (1.29–2.01)	308.3	1.40 (0.80–2.45)	217.8	1.49 (1.11–2.01)
Lung cancer mortality						
Surgery	83.6	1.00	166.4	1.00	73	1.00
SBRT	133.9	1.45 (0.97–2.16)	190.9	1.01 (0.40–2.56)	130.8	1.63 (0.95–2.79)

SBRT=stereotactic body radiotherapy