Published in final edited form as:
J Thorac Cardiovasc Surg. 2014 April ; 147(4): 1183–1192. doi:10.1016/j.jtcvs.2013.11.057.

Analysis of First Recurrence and Survival in Patients with Stage I Non-Small Cell Lung Cancer Treated with Surgical Resection or Stereotactic Radiation Therapy

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Abstract

Objectives—Comparative studies of survival between stereotactic body radiation therapy (SBRT) and surgery have been limited by lack of comparisons of recurrence patterns between matched cohorts in non-small cell lung cancer (NSCLC).

Methods—All patients undergoing treatment with surgery or SBRT for clinical Stage I NSCLC between June 2004-December 2010 were reviewed. Age, tumor characteristics, comorbidity score, pulmonary function, overall (OS) and disease free survival (DFS) and recurrence data were collected and propensity matching performed..

Results—The mean age for surgery (N=458) was 65.8 ± 10.5 vs. 74.4 ± 9.4 for SBRT (N=151) ($p<0.0001$). For the entire surgical cohort 3-year OS and DFS were 78% and 72%, respectively. For the entire SBRT cohort 3-year OS and DFS were 47% and 42%, respectively. The overall local recurrence rate for surgery was 2.6%. The overall local recurrence rate for SBRT was 10.7%. A propensity matched comparison based on age, tumor size, ACE comorbidity score, FEV1%, and tumor location resulted in 56 matched pairs. The 3-year overall survival was 52% vs. 68% for SBRT and surgery, respectively ($p=0.05$) while disease-free survival was 47% vs. 65% ($p=0.01$). At 3 years, local recurrence free survival was 90% vs. 92% for SBRT and surgery, respectively ($p=0.07$)

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Presented at the 93rd Annual Meeting of the American Association for Thoracic Surgery, Minneapolis MN, May 2013.

Conclusions—While surgical resection seems to result in better overall and disease free survival vs. SBRT, matching these disparate cohorts of patients remains challenging. Participation in clinical trials is essential to define the indications and relative efficacy of surgery and radiation therapy in a high-risk population with Stage I NSCLC.

Keywords

Stereotactic body radiation therapy; clinical stage I non-small cell lung cancer; ACE-27; propensity matching; lobectomy; sublobar resection

INTRODUCTION

Stereotactic body radiation therapy (SBRT) has become the primary treatment of choice for inoperable patients with peripheral stage I lung cancer. While the role of radiofrequency ablation (RFA) has yet to be defined for stage I lung cancer, single-center studies and a prospective trial of SBRT have consistently demonstrated good cancer-specific survival in patients deemed inoperable. [1–5] For SBRT, 3 year survival for stage I lung cancer has been reported to be 56%–85% with primary tumor local recurrence rates below 10% at 3 years. [3–8] These data have highlighted the benefit of this therapy in a cohort of patients that previously went untreated or were inadequately treated with conventional external beam radiation therapy.

Currently, surgical anatomic resection with mediastinal lymphadenectomy remains the standard of care for operable patients with stage I lung cancer. [9, 10] In the contemporary era of video assisted techniques (VATS) for anatomic resection, 5 year overall survival has been reported to be 75–80% with a perioperative mortality rate of 1%. [11–13] In small subsets of potentially operable patients from single center studies, SBRT has been associated with good primary tumor control and overall survival. While such findings are encouraging, these data are not sufficient to supplant surgical resection as the standard of care in the operable patient and clinical trials are needed to determine whether outcomes following SBRT are comparable to anatomic surgical resection. [2, 4, 14]

The ambiguous scenario, however, involves the so-called “high risk surgical patient” with early stage lung cancer. The ACOSOG (American College of Surgeons Oncology Group) Z4032 trial has recently examined the role of sublobar resection with and without brachytherapy in this subgroup of patients. [15] The ACOSOG Z4099/RTOG 1021 trial was an important prospective randomized trial designed to compare outcomes in high risk patients with stage I lung cancer treated with sublobar resection vs. SBRT. [16] Unfortunately, due to poor accrual, this trial was recently closed. Our institution has published previous comparative studies demonstrating comparable cancer-specific survival after surgery in propensity-matched groups of patients treated with either SBRT or surgery. [17–19] Limitations of previously published series include small sample size, inadequate follow up, inconsistent definitions of recurrence between the groups, and inadequate matching of the cohorts.

This study was designed to overcome some of the shortcomings of previously published comparisons. This is a retrospective propensity-matched comparative study utilizing a large

cohort of patients undergoing SBRT or surgical resection for stage I lung cancer. This study is designed to compare overall survival, disease-free survival, local recurrence, regional recurrence, and distant recurrence using common definitions of recurrence and survival from recent and ongoing clinical trials.

METHODS

This is a retrospective study of all patients undergoing treatment at our center with surgery or SBRT for clinical Stage I non-small cell lung cancer (NSCLC) between June 2004 and December 2010. The patients were treated at the Siteman Cancer Center, a National Cancer Institute designated comprehensive cancer center at the Washington University School of Medicine and Barnes-Jewish Hospital in Saint Louis, Missouri. All patients underwent clinical staging with CT and FDG-PET imaging. Patients were usually seen initially by a surgeon, and if considered high-risk for lobectomy were referred for SBRT. In the surgical patients, the type of surgical resection performed (i.e. lobar vs. sublobar), the type of incision, performance of mediastinoscopy, and extent of lymph node dissection was at the discretion of the treating thoracic surgeon. All surgical patients ultimately were confirmed to have non-small cell lung cancer (NSCLC) histologically. Patients undergoing SBRT did not undergo routine surgical staging with either mediastinoscopy or endobronchial ultrasound (EBUS).

All pre-treatment CT scans and FDG-PET scans were reviewed to include only those patients with clinical stage I lung cancer. Comorbidity scores were recorded prospectively using the Adult Co-Morbidity Evaluation (ACE-27) scoring system (Online supplemental Appendix 1). The Siteman Cancer Center Oncology Data Services in the Clinical Outcomes Research Office at Washington University prospectively assigns comorbidity scores.

Clinic and hospital charts, follow-up CT and FDG-PET scans, as well as follow-up biopsies were reviewed to determine local tumor recurrence, regional and distant recurrence, disease-free survival and overall survival. Patients were followed with serial chest radiographs and/or CT scans every 3–6 months for the first 2 years and every 6–12 months up to 5 years, then yearly afterward. FDG-PET imaging was performed if there was suspicion for recurrence. Local, regional, and distant recurrence definitions were as defined by the current clinical trial ACOSOG Z4099/RTOG 1021 trial for comparison of SBRT and sublobar resection in high risk patients. [20] Briefly, local recurrence included primary tumor site, marginal, ipsilateral lobar, or port site/wound recurrence. An important distinction in this trial is definition of local recurrence, which includes both primary tumor failure *and* (for sublobar resection or SBRT) failure in the involved lobe.. In some instances, the diagnosis of the first recurrence occurred simultaneously at different locations accounting for the multiple recurrences noted in some patients. Exclusion criteria included patients with small cell lung cancer or extra-thoracic cancers that metastasized to the lung, patients undergoing resection for benign disease, patients without preoperative staging chest CT and FDG-PET scans, patients with ≥T3 tumors and patients with clinical N1 or N2 disease noted on preoperative imaging. For the SBRT patients, every effort was made to obtain a tissue diagnosis prior to treatment. A small fraction (14%) of patients underwent treatment without a tissue diagnosis. These patients were reviewed at our multidisciplinary conference and in

all such patients, a radiologist reviewed the images and either attempted a biopsy or deemed a biopsy to be too high risk. These patients were included to demonstrate the practical management of clinical stage I lung cancer in high-risk/inoperable patients and to provide a reference to the proportion of patients treated without a tissue diagnosis relative to other published cohorts.

Details of SBRT planning and delivery at our institution have been described previously. [1] The Varian Trilogy System was used for all SBRT patients. Target coverage, conformality, and normal tissue constraints were followed according to the protocol for the clinical trial RTOG 0236. [8] Prescriptions were typically specified at the 60% to 90% (median 84%) isodose line so that ≥ 95% of the prescribed dose covered the planning target volume. Most SBRT patients received a biologically effective dose (BED) of at least 100 Gy_{10} (median dose, 54 Gy in 3 fractions). BED was calculated using $BED_{\alpha/\beta} = nd(1+ d/\alpha/\beta)$, where n = number of fractions, d = dose per fraction, and $\alpha/\beta = 10$ for tumor in line with prior reports. [6, 21]

BED_{10} for the SBRT regimens used in this study was 85.5 Gy_{10} (45 Gy in 5 fx, n= 6), 86.4 Gy_{10} (48 Gy in 6 fx, n=1), 100 Gy_{10} (50 Gy in 5 fx, n=21), 105.6 Gy_{10} (48 Gy in 4 fx, n=1), 112.5 Gy_{10} (45 Gy in 3 fx, n=6), 115.5 Gy_{10} (55 Gy in 5 fx, n=3), 132 Gy_{10} (60 Gy in 5 fx, n=4), and 151.2 Gy_{10} (54 Gy in 3 fx, n=110).

SAS Version 9.3 (Cary, NC) was used to perform all statistical analyses. Descriptive statistics included the mean ± standard deviation of continuous variables and counts and proportions of categorical data by group. Continuous and categorical variables were compared by a Kruskal-Wallis test and the X^2 test, respectively. Overall survival is defined from date of treatment to death date or the last follow-up. Disease-free was defined as being alive without disease. The patients with disease or death are counted as disease. DFS (Disease Free Survival) was defined as the time from date of treatment to date of cancer recurrence, death or last follow-up. Local, regional, or distant recurrence is defined as having local, regional, or distant failure, censored at any other recurrence or at last follow-up. Freedom from local, regional or distant recurrence is defined as the time from date of treatment to date of recurrence or last follow-up. Kaplan-Meier (KM) curves were generated that provide unadjusted survival estimates for patients across strata. Differences between strata were determined by log-rank tests. Based on previously published comparisons, an initial propensity matched analysis was performed to compare patients in the SBRT and surgery groups based on age, tumor stage, and ACE comorbidity score. To provide additional variables, a subsequent propensity score was estimated using age, FEV 1 (%), tumor size, tumor location and ACE comorbidity score. The matched pair is found using a caliper technique with a standard deviation defined as 0.075 of the estimated propensity score for both groups. All statistical tests were twosided using an $\alpha = 0.05$ level of significance.

The study and a waiver of informed consent were approved by the Washington University School of Medicine Human Research Protection Office.

RESULTS

Four hundred fifty eight patients underwent primary surgical resection for clinical stage I NSCLC and 151were treated with SBRT (Figure 1). Table 1 outlines demographics and preoperative comorbidity comparisons between the unmatched cohorts of surgery and SBRT patients. Surgery patients were younger and had lower comorbidity scores. Median follow up for the surgery cohort was 2.83 years while median follow up for the SBRT cohort was 1.95 years. There were 165 (36%) clinical T2 lesions in the surgery group vs. 41 (27%) in the SBRT group (p=0.0456). Pathologic N1 and N2 disease were identified in 11.8% (N=54) and 3.0% (N=14) of surgery patients. Additionally, 3.1% (N=14) of surgical patients were found to be pathologic T3, while 2.2% (N=10) were pathologic T4. Out of 293 clinical T1 lesions, 18.4% (54) were found to be pathologic T2. No patients in the SBRT cohort received adjuvant therapy while 17.5% (80) were confirmed to have received adjuvant therapy in the surgical cohort. Among surgical resections, 75.6% (N=347) underwent lobectomy, 5.9% (N=27) underwent pneumonectomy/bilobectomy, and 18.3% (N=84) underwent sublobar resection. Thirty day mortality was 1.09% (5/458) for the surgery group and 0.66% (1/151) for the SBRT group (p=NS). The cause of death in the single patient that died within 30 days of SBRT treatment was unknown and was defined as a sudden death.

Three year overall and disease-free survival for surgery was 78% and 72%, respectively (online supplemental Figure 1 and Table 1). Three year overall and disease-free survival for SBRT was 47% and 42%, respectively. Table 2 outlines the total proportion of local, regional, and distant recurrences for both cohorts. The overall local recurrence rate for surgery was 2.6%. The local recurrence rate for SBRT was 10.7%.

Surgical techniques were consistent over the duration of the study period. However, the dose of radiation administered for SBRT did change over time after identifying that doses less than 100 Gy_{10}were associated with higher local recurrence rates and worse overall survival in clinical studies. [21, 22] In this analysis only 7/151 patients received < 100 Gy_{10}, with no statistically significant difference in overall survival or local recurrence based upon the dose

Within the SBRT cohort, 14% of patients were treated without conclusive biopsy proof of cancer when an attempt at tissue diagnosis was unsuccessful, or when a needle biopsy was not pursued based on the perceived high risk of pneumothorax. There was no difference in overall survival or freedom from local recurrence among SBRT patients with or without a tissue diagnosis prior to treatment (Online Supplemental Figure 2. The majority of patients within the surgical cohort were treated with lobectomy (347/458, 75.8%). Pneumonectomy or bilobectomy was performed in 5.9% (27), and 18.3% (84) were treated with sublobar resection. Among the sublobar resections, 41.7% (35) were anatomical resections (segmentectomy) while 58.3% (49) were non-anatomical wedge resections. Tumor margin distance was not recorded in these patients. There was no difference in overall survival between the different types of resections performed. In the unmatched comparison, local recurrence rates following lobectomy, sublobar resection, and SBRT were 1.73% (N=6), 7.14% (N=6), and 10.67% (N=16), respectively (p<0.0001 lobectomy vs. SBRT, p=0.02 lobectomy vs. sublobar resection, p=0.5 sublobar resection vs. SBRT).

Among the 458 clinical stage I lung cancers, 14.8% (68/458) were upstaged at surgery and found to have occult N1 or N2 disease. For patients with occult nodal disease, 3- and 5-year overall survival was 66% and 43%, respectively. For patients without occult nodal disease, 3- and 5-year overall survival was 80% and 68%, respectively.

In an attempt to account for disparate cohorts, propensity matching was performed to identify two similar groups of patients within the SBRT and surgery cohorts for comparison. Age, ACE-27 and T status was used for propensity score estimation based on previous publications by us and others.[2,17,18] With the propensity matched model, 83 patients were matched from each of the cohorts. For the matched comparison, 3 year overall survival was 75% for surgery vs. 47% for SBRT ($p<0.0004$)(Online Supplemental Figure 3 and Table 3). Three year disease-free survival for surgery was 67% vs. 42% for SBRT ($p<0.0002$). Three year freedom from local recurrence for the surgical cohort was 97% vs. 90% for the SBRT cohort ($p<0.01$). Three year freedom from regional recurrence and from distant recurrence did not differ between the matched cohorts.

DISCUSSION

The development and more widespread use of ablative nonoperative treatment modalities for stage I NSCLC such as SBRT and radiofrequency ablation have prompted us to further evaluate the role of these therapies relative to surgical resection. Comparative studies of these modalities have been limited in number and are often difficult to interpret due to variability in methodological issues. While this current study is retrospective we have attempted to rigorously compare SBRT and surgical resection in stage I NSCLC outcomes utilizing strictly defined local and regional recurrence criteria accepted by National Cancer Institute co-operative groups. [20] These data highlight the challenges and limitations of attempting to match disparate groups of patients retrospectively for a comparative survival analysis. The final matched analysis included one third of the original SBRT cohort and one ninth of the surgery cohort. This final matched comparison suggests improved OS and DFS with surgery vs. SBRT with a trend towards improved local recurrence free survival, albeit not statistically significant in this small cohort.. Despite our efforts to match patients retrospectively it remains difficult to objectively define which subset of high-risk patients would benefit from one modality vs. the other. Overall survival is expectedly better in unmatched surgical patients compared to SBRT treated patients generally because of a higher burden of comorbidities in the SBRT cohort. Likewise, despite our efforts at matching patients, other unmeasured covariates may be taken into consideration when deeming a patient to be fit for surgery. One variable included in the final matched comparison was pre-treatment FEV1%, which was documented in only 62% of SBRT treated patients vs. 97% of surgical patients. This, therefore, excludes a number of patients in the SBRT group that are available for comparison (i.e. N=56) compared to our initial matched comparison that included age, tumor stage, and comorbidity score (i.e. N=83). While FEV1% is frequently utilized to risk stratify surgical patients, the exclusion of this variable in a significant number of SBRT treated patients highlights the fact that other potentially unmeasured covariates may weigh in the decision to pursue nonoperative treatment at our institution..

In previously published studies, cancer specific survival has been similar in matched cohorts of patients. [7, 19, 23, 24] Given that the ACOSOG/RTOG randomized trial utilized overall survival and disease-free survival endpoints, we elected to utilize these endpoints. We recognize that they may be considered biased for surgical treatment as non-cancer related mortality may occur more frequently in very high risk patients undergoing SBRT. Alternatively, cause specific survival is a favored endpoint for treatment modalities when patients have a high likelihood of mortality from associated comorbidities. While survival outcomes seem intuitive, the consistent use of similar outcome measures for surgically treated patients and SBRT treated patients will be important in future comparative studies.

Given the median follow up of 2.8 years and a predominance of lobar resections, the local recurrence rate of 2.6% is similar to other reported series of comparable surgical resections. [11, 25] A previous publication from our institution excluding sublobar resections demonstrated similar postoperative recurrence patterns. [24] True local recurrence after lobectomy would likely be limited to a stump recurrence. Higher “local recurrence” rates have been reported within the surgical literature sometimes attributed to inclusion of all locoregional recurrences within the local recurrence definition. [26] Surgical cohorts with a larger proportion of non-anatomic sublobar resections may also result in a higher reported local recurrence rate as staple line recurrence would occur with greater frequency. Inclusion of more central lesions requiring pneumonectomy/bilobectomy may result in a higher reported local recurrence rate although this represented a small proportion of resections in this study.

The overall local recurrence rate following SBRT was 10.7% in this series. Within the SBRT literature, various definitions of recurrence have been utilized to report outcomes from a focal ablative therapy. Recurrence outcomes may include primary tumor site recurrence, marginal recurrence, or intralobar recurrence. [4, 8, 24, 27] Recognizing the variability in the definitions of recurrence in both the SBRT and surgical literature, we felt that one of the strengths of this report is that similar criteria were utilized to define local recurrence between the 2 cohorts. A potential criticism of this analysis is that we chose to limit our evaluation of recurrence to first recurrence, a commonly reported endpoint in the surgical literature.

Anatomic resection, particularly lobectomy, has been associated with excellent long-term survival ranging from 65–80% for stage I NSCLC. [10–12, 28] Furthermore, contemporary series of minimally invasive lobectomy have been associated with minimal perioperative mortality and 5 year overall survival ranging from 75–90%. [11, 12, 29] While ongoing surgical trials attempt to identify the role of sublobar resection in stage I lung cancer, the predominance of lobectomy in this series highlights our institutional bias towards lobar resection, reserving sublobar resection for high risk patients with poor pulmonary reserve. An ongoing challenge with clinical trials, as well as within clinical practice is that current guidelines defining the high risk patient are subjective and prone to physician bias. A recent secondary analysis of clinical trial inclusion criteria for SBRT underscored this bias by demonstrating that many patients that were considered inoperable were perhaps reasonable surgical candidates. [30] In the absence of a clinical trial or a prospective database, there is currently no objective algorithm to guide the assignment of surgery versus SBRT.

Attempts to objectively stratify risk within the surgical population have been challenging. Other published work at our institution has suggested that the Charlson Comorbidity Score may serve as a better measure of comorbidity than the ACE score in these populations [31]. Other risk models based on the European Thoracic Database and the Society of Thoracic Surgeons Database have attempted to model perioperative morbidity, length of stay and assessment of quality of care in thoracic surgery across all surgical patients. These models are not yet robust enough to guide decision-making regarding treatment assignment or classification of the very high risk surgical patient where alternative therapies may be preferable. [32–34] In conjunction with this, alternative outcome measures such as toxicity, quality of life, and functional capacity after treatment need to be important components of comparative studies. As comorbidity increases and life expectancy decreases, it is quite reasonable to presume that patient reported outcomes such as health-related quality of life will take on higher importance as compared to absolute overall survival. We must be cognizant that patients may be willing to sacrifice some long term survival benefit related to surgery for a potential preservation of quality of life that may be presumed to be associated with SBRT treatment. Any attempt to construct an algorithm to guide treatment decisions in these patients must pay attention to patient preferences and the factors that guide such preferences.

In this study 14.8% of clinical stage I patients were ultimately found to have nodal disease at resection with a 5-year overall survival of 43%. Given current clinical staging techniques, some patients with involved nodes are likely missed in the SBRT group. Our reported incidence of occult nodal disease following resection in these clinical stage I patients is similar to that observed in other reports. [11, 17] Overall, 19.4% of clinical stage I patients treated with surgery were eventually shown to be pathologic stage II, III, or IV. Furthermore patients with a higher T stage than clinically predicted may also impact local recurrence rates in the SBRT treated patients. Future improvements in clinical staging with identification of occult nodal or metastatic disease may allow for earlier use of adjuvant treatment in SBRT treated patients.

This study presents a concerted effort to utilize trial based guidelines to compare outcomes between different treatment modalities in patients with stage I lung cancer. This work highlights some of the current limitations of retrospective comparative studies in disparate populations. The apparent advantages of surgery in terms of overall and disease free survival and potentially local recurrence will still need to be confirmed in a prospective, randomized fashion. A reasonable goal for work like this would be to improve our ability to draw on objective data to guide the allocation of appropriate treatment in stage I lung cancer patients at increased risk for perioperative death and surgical complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Research reported in this publication was supported by the Washington University Institute of Clinical and Translational Sciences grant UL1 TR000448 from the National Center for Advancing Translational Sciences

(NCATS) of the National Institutes of Health (NIH). The content is solely the responsibility of the authors and does not necessarily represent the official view of the NIH.

Abbreviations

NSCLC	Non-Small Cell Lung Cancer
SBRT	stereotactic body radiation therapy
OS	overall survival
DFS	Disease Free Survival
ACOSOG	American College of Surgeons Oncology Group
RTOG	Radiation Therapy Oncology Group
RFA	radiofrequency ablation
FDG-PET	2-deoxy-2[F-18]fluoro-D-glucose positron emission tomography
ACE-27	Adult Comorbidity Evaluation-27
BED	Biologic Effective Dose
EBUS	Endobronchial Ultrasound

REFERENCES

1. Bradley JD, 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(4):1146–1150. [PubMed: 19800181]
2. Lagerwaard FJ, 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. 2011
3. Lagerwaard FJ, 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(1):348–353. [PubMed: 22104360]
4. Onishi H, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys. 2011; 81(5):1352–1358. [PubMed: 20638194]
5. Shibamoto Y, et al. Stereotactic body radiotherapy using a radiobiology-based regimen for stage I nonsmall cell lung cancer: a multicenter study. Cancer. 2012; 118(8):2078–2084. [PubMed: 22009495]
6. Onishi H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer. 2004; 101(7):1623–1631. [PubMed: 15378503]
7. Ricardi U, et al. Stereotactic body radiation therapy for early stage non-small cell lung cancer: results of a prospective trial. Lung Cancer. 2010; 68(1):72–77. [PubMed: 19556022]
8. Timmerman R, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA. 2010; 303(11):1070–1076. [PubMed: 20233825]
9. Darling GE, et al. Number of lymph nodes harvested from a mediastinal lymphadenectomy: results of the randomized, prospective American College of Surgeons Oncology Group Z0030 trial. Chest. 2011; 139(5):1124–1129. [PubMed: 20829340]
10. 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(3):615–622. discussion 622–3. [PubMed: 7677489]

11. Flores RM, et al. Patterns of recurrence and incidence of second primary tumors after lobectomy by means of video-assisted thoracoscopic surgery (VATS) versus thoracotomy for lung cancer. J Thorac Cardiovasc Surg. 2011; 141(1):59–64. [PubMed: 21055770]
12. McKenna RJ Jr. New approaches to the minimally invasive treatment of lung cancer. Cancer J. 2005; 11(1):73–76. [PubMed: 15831227]
13. Paul S, et al. Thoracoscopic lobectomy is associated with lower morbidity than open lobectomy: a propensity-matched analysis from the STS database. J Thorac Cardiovasc Surg. 2010; 139(2):366–378. [PubMed: 20106398]
14. Louie AV, et al. Stereotactic body radiotherapy versus surgery for medically operable Stage I non-small-cell lung cancer: a Markov model-based decision analysis. Int J Radiat Oncol Biol Phys. 2011; 81(4):964–973. [PubMed: 20932688]
15. Fernando HC, et al. Thirty- and ninety-day outcomes after sublobar resection with and without brachytherapy for non-small cell lung cancer: results from a multicenter phase III study. J Thorac Cardiovasc Surg. 2011; 142(5):1143–1151. [PubMed: 21872277]
16. Fernando HC, Timmerman R. American College of Surgeons Oncology Group Z4099/Radiation Therapy Oncology Group 1021: a randomized study of sublobar resection compared with stereotactic body radiotherapy for high-risk stage I non-small cell lung cancer. J Thorac Cardiovasc Surg. 2012; 144(3):S35–S38. [PubMed: 22795435]
17. Crabtree TD, et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. J Thorac Cardiovasc Surg. 2010; 140(2):377–386. [PubMed: 20400121]
18. Puri V, et al. A comparison of surgical intervention and stereotactic body radiation therapy for stage I lung cancer in high-risk patients: A decision analysis. J Thorac Cardiovasc Surg. 2012; 143(2):428–436. [PubMed: 22169443]
19. Robinson CG, et al. Outcomes after Stereotactic Body Radiation Therapy (SBRT) or Anatomic Surgical Resection (ASR) for Clinical Stage I Non-small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2010; 78(3):S15.
20. [cited 2013 April 15] Surgery With or Without Internal Radiation Therapy Compared With Stereotactic Body Radiation Therapy in Treating Patients With High-Risk Stage I Non-Small Cell Lung Cancer. Available from: www.clinicaltrials.gov.
21. Olsen JR, et al. Dose-response for stereotactic body radiotherapy in earlystage non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2011; 81(4):e299–e303. [PubMed: 21477948]
22. Onishi H, 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(7 Suppl 3):S94–S100. [PubMed: 17603311]
23. Andratschke N, et al. Stereotactic radiotherapy of histologically proven inoperable stage I non-small cell lung cancer: patterns of failure. Radiother Oncol. 2011; 101(2):245–249. [PubMed: 21724287]
24. Robinson CG, et al. Patterns of failure after stereotactic body radiation therapy or lobar resection for clinical stage I non-small-cell lung cancer. J Thorac Oncol. 2013; 8(2):192–201. [PubMed: 23287852]
25. Martini N, et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. J Thorac Cardiovasc Surg. 1995; 109(1):120–129. [PubMed: 7815787]
26. Kelsey CR, et al. Local recurrence after surgery for early stage lung cancer: an 11-year experience with 975 patients. Cancer. 2009; 115(22):5218–5227. [PubMed: 19672942]
27. Senthi S, et al. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. Lancet Oncol. 2012; 13(8):802–809. [PubMed: 22727222]
28. Goldstraw P, 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(8):706–714. [PubMed: 17762336]
29. Flores RM, et al. Lobectomy by video-assisted thoracic surgery (VATS) versus thoracotomy for lung cancer. J Thorac Cardiovasc Surg. 2009; 138(1):11–18. [PubMed: 19577048]
30. Crabtree T, 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(3):692–699. [PubMed: 23174176]

31. DeWees TA, et al. Defining Optimal Comorbidity Measures for Patients With Medically Inoperable Early-stage Non-small Cell Lung Cancer (NSCLC) Treated With Stereotactic Body Radiation Therapy (SBRT). Int J Radiat Oncol Biol Phys. 2012; 84(3):S172.
32. Brunelli A, et al. The European Thoracic Database project: composite performance score to measure quality of care after major lung resection. Eur J Cardiothorac Surg. 2009; 35(5):769–774. [PubMed: 19272784]
33. Kozower BD, et al. STS database risk models: predictors of mortality and major morbidity for lung cancer resection. Ann Thorac Surg. 2010; 90(3):875–881. discussion 881–3. [PubMed: 20732512]
34. Wright CD, et al. Predictors of prolonged length of stay after lobectomy for lung cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database risk-adjustment model. Ann Thorac Surg. 2008; 85(6):1857–1865. discussion 1865. [PubMed: 18498784]

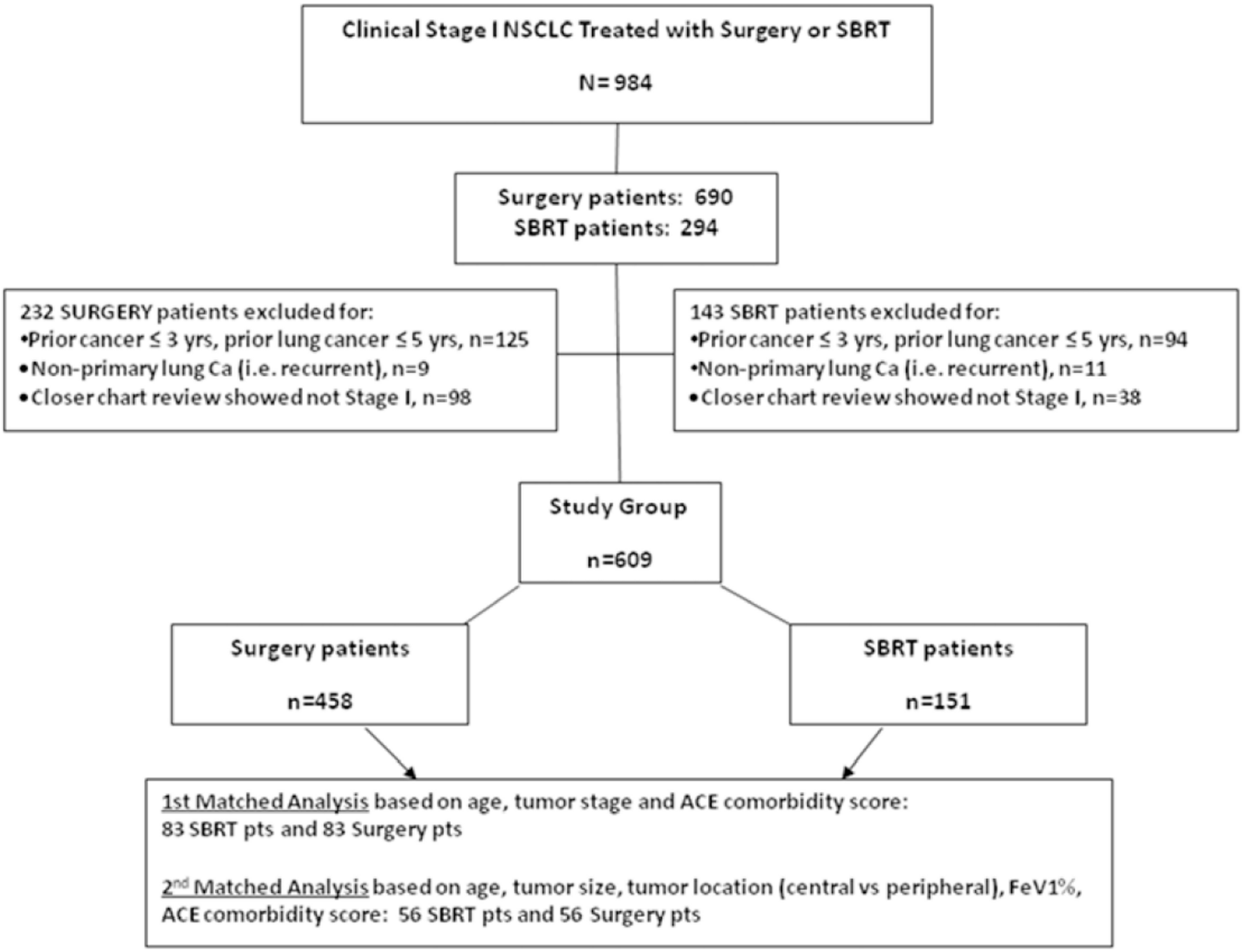

Figure 1.

CONSORT diagram outlining selection of patients treated with either SBRT or surgery for Stage I Non-small cell lung cancer.

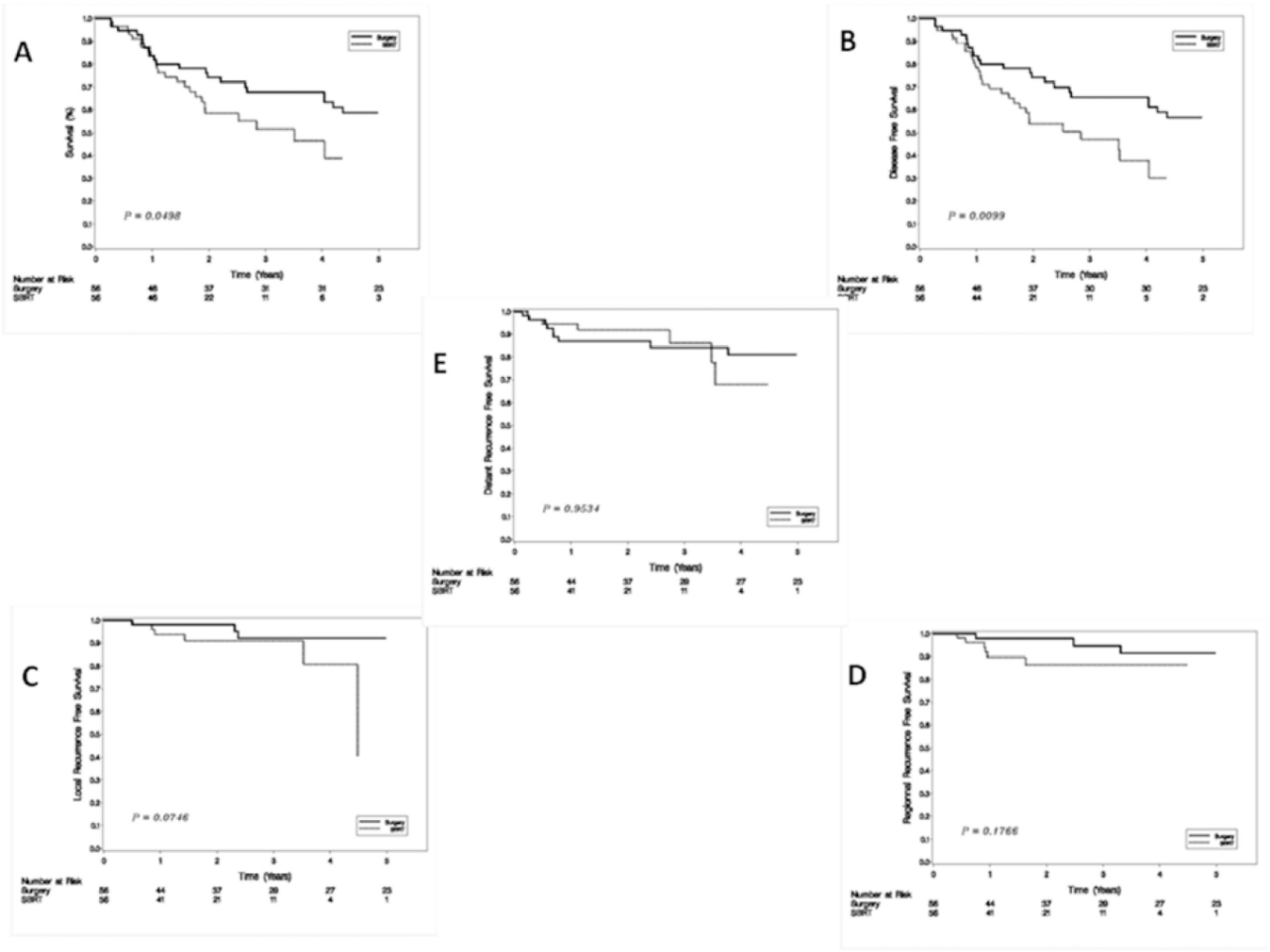

Figure 2.

Overall survival, disease free-survival and freedom from local, regional and distant recurrence between the matched cohorts of surgical and SBRT patients matched for age, tumor size, tumor location, FEV1%, and ACE comorbidity score. Final propensity matching resulted in 56 patients in each cohort.

Table 1

Patient and Disease Characteristics for Unmatched Patients

Variable	SBRT (N=151)	Surgery (N=458)	p-value[1]
Age, years (mean ± SD)	74.4 ± 9.4	65.8 ± 10.5	<.0001
Age>75 years (%)	73 (48.3)	89 (19.4)	<.0001
Male (%)	80 (53.0)	212 (46.3)	0.1535
Race[2]			0.9686
White	132 (88.0)	403 (88.0)	
Black	16 (10.7)	50 (10.9)	
Asian	2 (1.3)	5 (1.1)	
Weight (lb) [3]	173.5 ± 49.1	172.7 ± 46.0	0.7391
T2 (%)	41 (27.2)	165 (36.0)	0.0456
CM Score (%) [2]			<.0001
0 – 1	37 (32.7)	268 (64.1)	
2 – 3	76 (67.3)	150 (35.9)	
Smoking[2]			0.2567
Yes	126 (85.1)	406 (88.7)	
No	22 (14.9)	52 (11.4)	
Hypertension[3]			0.7003
Yes	90 (63.4)	136 (65.4)	
No	52 (36.6)	72 (34.6)	
Size of Tumor	2.6 ± 1.0	2.9 ± 1.7	0.4522
Location of Tumor			<.0001
Peripheral	122 (84.1)	277 (66.4)	
Central	23 (15.9)	140 (33.6)	
FEV1 (mean ± SD) [3]	1.4 ± 0.7 (n=95)	2.1 ± 0.8(n=449)	<.0001
FEV1 (%) (mean ± SD) [3]	57 ± 25 (n=94)	79 ± 20(n=444)	<.0001
DLCO (mean ± SD) [3]	10.8 ± 4.9 (n=59)	16.2 ± 6.2(n=387)	<.0001
DLCO (%) (mean ± SD) [3]	53 ± 24 (n=67)	74 ± 25(n=382)	<.0001
Surgery Procedure Type (%)			
Bilobectomy	NA	10 (2.2)	
Lobectomy		347 (75.8)	
Pneumonectomy		17 (3.7)	

Variable	SBRT (N=151)	Surgery (N=458)	p-value[1]
Segmentectomy		35 (7.6)	
Wedge		49 (10.7)	

Abbreviations: SD, standard deviation;

[1] Chi-square or Fisher Exact test for categorical variable; Kruskal-Wallis Test for continuous variable.

[2] The denominator for the percentages is the sum of patients across all categories in the SBRT or Surgery group, respectively, excluding missing values.

[3] High frequency of Missing values;

Table 2

Total Proportion of Local, Regional, and Distant Recurrences Occurring in All Patients with Stage 1 NSCLC Treated with Surgery or SBRT

	NO Recurrence	Local Recurrence	Regional Recurrence	Distant Recurrence
Surgery	77.7%	2.6%	7.0%	12.7%
SBRT	66%	10.7%	10%	13.3%

Table 3

Patient and Disease Characteristics for Matched Patients[*]

Variable	SBRT (N=56)	Surgery (N=56)	p-value[1]
Age, years (mean ± SD)	70.7 ± 10.6	70.0 ± 8.1	0.6496
Age>75 years (%)	20 (35.7)	16 (28.6)	0.4183
Male (%)	29 (51.8)	32 (57.1)	0.5692
Race[2]			0.3207
White	49 (89.1)	53 (94.6)	
Black	6 (10.9)	3 (5.4)	
Weight (lb) [3]	175.6 ± 54.5	164.3 ± 44.1	0.3355
T2 (%)	16 (28.6)	24 (42.9)	0.1147
CM Score (%)			0.5702
2 – 3	31 (55.4)	28 (50.0)	
Smoking[2]			0.2060
Yes	51 (92.7)	55 (98.2)	
No	4 (7.3)	1 (1.8)	
Hypertension[2]			0.6989
Yes	33 (62.3)	6 (75.0)	
No	20 (37.7)	2 (25.0)	
Size of Tumor	2.5 ± 1.1	3.0 ± 1.6	0.3095
Location of Tumor			0.3408
Peripheral	49 (87.5)	52 (92.9)	
Central	7 (12.5)	4 (7.1)	
FEV1 (mean ± SD) [3]	1.6 ± 0.7	1.6 ± 0.6	0.6156
FEV 1(%) (mean ± SD)	64 ± 24	62 ± 18	0.8522
DLCO (mean ± SD) [3]	11.6 ± 5.3	14.3 ± 4.8	0.0020
DLCO (%) (mean ± SD) [3]	55 ± 20	73 ± 27	0.0001
Surgery Procedure Type (%)			
Bilobectomy	NA	1 (1.8)	
Lobectomy		44 (78.6)	
Pneumonectomy		0	
Segmentectomy		6 (10.7)	
Wedge		5 (8.9)	

[*] Age, comobidity score, FEV 1 (%), tumor location, and tumor size were used for propensity score estimation. c-statistics is 0.824. The matched pair is found using a caliper technique with a standard deviation defined as 0.075 of the estimated propensity score for both groups.

Abbreviations: SD, standard deviation; NA, not applicable.

[1] Chi-square or Fisher Exact test for categorical variable; Kruskal-Wallis Test for continuous variable.

[2] The denominator for the percentages is the sum of patients across all categories in the SBRT or Surgery group, respectively, excluding missing values.

[3] Missing values;