Title

Association of Operability With Post-Treatment Mortality in Early-Stage Non-Small Cell Lung Cancer.

Journal

Clinical Lung Cancer, 23(3)

Authors

Stokes, William
Xiong, Niya
Liu, Yuan
et al.

Publication Date

2022-05-01

DOI

10.1016/j.cllc.2021.12.012

Peer reviewed

HHS Public Access

Author manuscript

Clin Lung Cancer. Author manuscript; available in PMC 2023 May 01.

Published in final edited form as:

Clin Lung Cancer. 2022 May ; 23(3): e231–e237. doi:10.1016/j.cllc.2021.12.012.

Association of Operability with Post-Treatment Mortality in Early-Stage Non-Small Cell Lung Cancer

William A. Stokes, MD[a,b,*], **Niya Xiong, MS**[c,d], **Yuan Liu, PhD**[a,c], **Kristin A. Higgins, MD**[a,b], **Sibo Tian, MD**[a,b], **Jeffrey D. Bradley, MD**[a,b], **Drew Moghanaki, MD MPH**[e], **Chad G. Rusthoven, MD**[f]

[a]Winship Cancer Institute, Emory University

[b]Department of Radiation Oncology, Emory University School of Medicine

[c]Department of Biostatistics and Bioinformatics, Emory University School of Medicine

[d]Department of Data Science, Dana Farber Cancer Institute *(current institutional affiliation)*

[e]Department of Radiation Oncology, David Geffen School of Medicine at University of California Los Angeles

[f]Department of Radiation Oncology, University of Colorado School of Medicine

Abstract

MicroAbstract: We evaluated the association of operability status with early post-treatment mortality among patients with early-stage non-small cell lung cancer undergoing stereotactic body radiotherapy. In this cohort study of 80,108 patients from a large US cancer dataset, operable patients undergoing stereotactic body radiotherapy experienced <1% risk of mortality through 90 days post-treatment, significantly lower than corresponding rates observed among their inoperable counterparts. These findings imply that non-randomized comparisons of surgical versus non-surgical approaches for early-stage non-small cell lung cancer are vulnerable to confounding by operability and should be interpreted with caution.

Clinical Practice Points: Operability status is increasingly understood to independently predict long-term survival outcomes in early-stage NSCLC; however, it is unknown what impact this important confounder exerts in the early post-treatment time period. We performed a retrospective

[*]Corresponding Author: William A. Stokes, MD, Emory University School of Medicine, Glenn Building, 550 Peachtree St NE, Atlanta, GA 30308, wastoke@emory.edu.

William A. Stokes, MD, Conceptualization, Methodology, Writing - review & editing, Visualization, Niya Xiong, MS, Methodology, Formal analysis, Data curation, Yuan Liu, PhD, Methodology, Software, Formal analysis, Resources, Data curation, Kristin A. Higgins, MD, Writing - review & editing, Sibo Tian, MD, Methodology, Writing - review & editing, Jeffrey D. Bradley, MD, Writing - review & editing, Drew Moghanaki, MD MPH, Conceptualization, Writing - review & editing, Chad G. Rusthoven, MD, Conceptualization, Methodology, Writing - review & editing

Author Contributions

All authors made substantial contributions to design or interpretation of the work, drafted or revised the manuscript for intellectual content, provided final approval for the submitted version, and agree to be accountable for all aspects of the work.

Declarations of Interest

none

cohort study of over 80,000 patients undergoing surgery and stereotactic body radiotherapy for early-stage NSCLC and evaluated post-treatment mortality at 30, 60, and 90 days post-treatment. We found that operable SBRT patients experience very low rates of post-treatment mortality (<1%) that compare favorably both to those of inoperable SBRT patients (2.9%) and to those of surgically treated patients (≥2.4%). These findings illustrate the profound and early influence of confounding by operability in non-randomized comparisons.

Background: Operability is both a crucial determinant in treatment selection and a potential confounder in analyses comparing surgery with non-surgical approaches such as stereotactic body radiotherapy (SBRT). We aimed to assess the association between operability status and intervention with post-treatment mortality in early-stage non-small cell lung cancer (NSCLC).

Patients and Methods: We defined four groups of patients with cT1-T2N0M0 NSCLC diagnosed 2010–2014 from the National Cancer Database: SBRT patients deemed operable versus inoperable and surgery patients receiving open versus minimally-invasive approaches. Mortality rates at 30, 60, and 90 days (d) post-treatment were calculated and compared.

Results: We abstracted 80,108 patients, 0.8% undergoing SBRT and operable, 13.2% undergoing SBRT and inoperable, 52.4% undergoing open surgery, and 33.7% undergoing minimally-invasive surgery. Mortality rates were highest among open surgery patients and lowest among operable SBRT patients (2.0% vs 0.2% at 30d and 3.7% vs 0.7% at 90d), with intermediate results in the other two groups. These findings persisted on multivariate Cox regression: compared to patients undergoing minimally-invasive surgery, mortality risk was highest among open surgery patients (30d HR 1.32, 95%CI 1.16–1.51; 90d HR 1.36, 95%CI 1.24–1.50; both $p<0.001$) and lowest among operable SBRT patients (30d HR 0.09, 95%CI 0.01–0.64; 90d HR 0.15, 95%CI 0.05–0.46; both $p\leq0.016$). These associations were maintained in a propensity score-matched subset.

Conclusion: Operable patients undergoing SBRT experience minimal post-treatment mortality compared to their inoperable counterparts. These findings illustrate the potential for confounding by operability to bias results in cohort studies that compare surgical versus non-surgical approaches in early-stage NSCLC.

Keywords

non-small cell lung cancer; SBRT; confounding; confounding by operability; confounding by indication

Introduction

Increases in human longevity and the advent of effective screening[1] are contributing to a growing incidence of early-stage non-cell lung cancer (NSCLC).[2] While anatomic lung resection remains the preferred management approach for eligible individuals confronting this diagnosis,[3–5] favorable outcomes with stereotactic body radiotherapy (SBRT) in inoperable patients have spurred interest in directly comparing surgery with SBRT in operable patients. Multiple prospective randomized trials comparing these approaches have failed to reach target accrual. To date, the only available randomized comparison consists of a single combined analysis of two such trials.[6] While this analysis demonstrated encouraging disease control and survival outcomes with both treatments, these findings

are far from conclusive due to the pooling of data from distinct trials, the small analytic cohort of 58 patients, and limited use of minimally-invasive surgical techniques such as video-assisted thoracoscopic surgery (VATS).

In the absence of robust prospective comparative data, multiple retrospective analyses have compared outcomes between patients treated with surgery and those treated with SBRT. The vast majority of these have not incorporated operability status as an inclusion criterion or covariate. This serial omission introduces the potential for confounding by indication,[7,8] with operability serving as a confounding factor that influences both exposure (surgery versus SBRT) and outcome (survival).

Findings from several analyses illustrate the importance of operability among patients treated exclusively with SBRT. Collectively, these studies demonstrate superior long-term outcomes among operable patients as compared to their inoperable counterparts.[9–12] However, patients considering SBRT may prioritize more immediate endpoints,[13] and the impact of operability status on short-term outcomes is poorly understood. This knowledge gap presents a barrier to shared decision-making between patients and providers and highlights the need for additional data.

We aimed to assess the impact of operability status on post-treatment mortality in a large contemporary cohort of patients undergoing SBRT and surgery for early-stage NSCLC.

Patients and Methods

The National Cancer Database (NCDB), a joint project of the Commission on Cancer (CoC) of the American College of Surgeons (ACS) and the American Cancer Society, is a hospital-based registry that captures approximately 70% of incident cancer cases in the United States and collects data from over 1,500 CoC-accredited cancer programs. The NCDB contains detailed information on demographic, clinical, and treatment-related factors. The ACS and the CoC have not verified and are not responsible for the analytic or statistical methodology used or for the conclusions drawn from these data by the investigators. This study was performed with the approval of our local institutional review board.

The NCDB was initially queried for patients diagnosed with NSCLC between 2004 and 2015 (Supplementary Figure 1). We excluded 657,056 patients diagnosed prior to 2010 (before which minimally-invasive surgery and surgical refusal were not recorded), 177,756 with prior diagnoses of malignancy, and 423,684 with clinical stage other than T1-T2N0M0. Next, we excluded 1,430 patients undergoing surgical procedures other than wedge resection, sublobar resection, lobectomy, or bilobectomy or resections of unknown extent (1,430). For non-surgical patients we included only those receiving SBRT to a thoracic target with complete information about surgical disposition, thereby excluding 28,122 patients. In parallel, for patients undergoing surgery we included only those without neoadjuvant radiotherapy and with complete information about surgical approach, thereby excluding 5,375 patients. Finally, 19,502 patients without OS data were excluded, including all cases diagnosed in 2015. Applying these criteria yielded a final analytic cohort of 80,108 patients.

Patients undergoing SBRT were further divided into “operable” and “inoperable” groups based on their recorded “reason for no surgery”, with patients who were offered but declined surgery deemed “operable”. Patients undergoing surgery were further divided into “minimally-invasive” or “open” groups according to whether or not they were recorded as undergoing a minimally-invasive surgical approach. This yielded four groups for comparison: open surgery, minimally-invasive surgery, SBRT operable, and SBRT inoperable.

The primary outcomes of this analysis were 30-day, 60-day, and 90-day mortality, measured in days from intervention (either definitive surgery or radiation start). Any patient with recorded follow-up or death beyond a given time point was considered alive at that time point, while any with follow-up ending prior to the time point of interest was censored. Covariates of interest included age, year of diagnosis, gender, race, insurance status, income quartile, facility type, comorbidity score, primary anatomic lobe, clinical T-classification, and histology.

Statistical Analysis

Statistical analyses were conducted using SAS Version 9.4, and SAS macros developed by the Biostatistics and Bioinformatics Shared Resource at Winship Cancer Institute.[14] The level of statistical significance was set at $p<0.050$ by two-sided test. Descriptive statistics for each variable were reported. The univariable association with study group was carried out by χ^2-squared test for categorical covariates and by ANOVA for numerical covariates. The univariable association or multivariable modeling with OS was conducted by proportional hazard model with hazard ratio (HR) and its 95% confidence interval (95%CI) being reported. Multivariable models were built by backward elimination steps with an alpha level of removal of 0.05. Product limit estimator for time to failure and log-rank test were used to depict the mortality pattern within 30-, 60-, or 90-day after treatment started.

The generalized propensity score[15] was estimated for the four study groups by multinomial logistic regression treating the comparison groups as the outcome and baseline covariates as predictors (age, year of diagnosis, gender, race, insurance, income, facility type, comorbidity score, primary site, clinical T-classification, histology). A generalized propensity score matching (PSM) algorithm[16] was applied to create a pseudo-sample where all covariates of interest are balanced among the comparison groups. The covariate balance was checked before and after PSM by the standardized difference, with value < 0.2 considered an acceptable imbalance.[17] The association with survival outcome was examined in the final matched sample.

Results

Of the 80,108 patients in the analytic cohort, 41,946 (52.4%) underwent open surgery, 26,963 (33.7%) underwent minimally-invasive surgery, 10,593 (13.2%) underwent SBRT and were inoperable, and 606 (0.8%) underwent SBRT and were deemed operable.

There were statistically significant baseline differences among these groups (Table 1). Comparing the two SBRT with the two surgery groups, the largest differences were that

SBRT patients were older and more likely to have Medicare insurance and squamous cell carcinoma histology. Between surgical groups, those undergoing minimally-invasive techniques were more likely to be diagnosed in later years, to be female, to reside in high-income areas, and to receive care at academic centers. Between SBRT groups, operable patients were slightly older and more likely to undergo care at non-academic facilities and to have lower comorbidity burdens.

Crude mortality estimates at 30 days, 60 days, and 90 days are depicted in Figure 1A and Table 2. At each time point, the highest mortality rates were observed among patients undergoing open surgical approaches (2.0% at 30 days, 3.0% at 60 days, and 3.7% at 90 days), and the lowest rates were observed among SBRT patients deemed operable (0.2% at 30 days, 0.3% at 60 days. and 0.7% at 90 days), all $p<0.001$. Mortality rates for minimally-invasive surgery patients (1.3% at 30 days, 2.0% at 60 days, 2.4% at 90 days) and inoperable SBRT patients (0.5% at 30 days, 1.6% at 60 days, 2.9% at 90 days) fell in between these extremes.

In the multivariable Cox regression models, all covariates except race were included after backwards elimination (Supplementary Table 1). As compared to patients undergoing minimally invasive surgery, the risk of mortality was statistically significantly higher among patients undergoing open surgery at 30 days (HR 1.32, 95%CI 1.16–1.51, $p<0.001$), 60 days (HR 1.34, 95%CI 1.20–1.49, $p<0.001$), and 90 days (HR 1.36, 95%CI 1.24–1.50, $p<0.001$); however, this risk was statistically significantly lower for patients undergoing SBRT, whether inoperable (HR 0.27, 95%CI 0.20–0.36 at 30 days; HR 0.54, 95%CI 0.45–0.65 at 60 days; HR 0.82, 95%CI 0.71–0.95 at 90 days, all $p\leq0.007$) or operable (HR 0.09, 95%CI 0.01–0.90 at 30 days; HR 0.12, 95%CI 0.03–0.47 at 60 days; HR 0.15, 95%CI 0.05–0.46 at 90 days, all $p\leq0.016$).

Additional factors associated with increased risk of mortality at each time point were increasing age, uninsured or unknown insurance status, lower income, high comorbidity burden, T2 classification, and squamous cell carcinoma histology (Supplementary Table 1). Conversely, female gender, private insurance, academic facility type, and anatomic location in the left lower or right middle lobe were independently associated with reduced risk of mortality.

PSM yielded four well-balanced groups of 593 patients apiece (Supplementary Figure 2). As in the overall cohort, the highest mortality rates were observed among patients undergoing open surgical approaches (1.9% at 30 days, 3.9% at 60 days, and 4.6% at 90 days), and the lowest rates were observed among operable SBRT patients (0.2% at 30 days, 0.3% at 60 days. and 0.5% at 90 days), all $p\leq0.032$ (Figure 1B, Table 3). As compared to those patients undergoing minimally-invasive surgery, univariable Cox regression demonstrated statistically significantly lower risk of mortality among operable SBRT patients (HR 0.11, 95%CI 0.01–0.87 at 30 days; HR 0.13, 95%CI 0.03–0.58 at 60 days; HR 0.14, 95%CI 0.04–0.47 at 90 days, all $p\leq0.037$). This risk was not statistically significantly different for patients undergoing open surgical approaches or those undergoing SBRT deemed inoperable (Supplementary Table 2).

Discussion

This study characterizes the associations of operability status and intervention with post-treatment mortality among individuals undergoing definitive therapy for early-stage NSCLC. Operable patients undergoing SBRT experienced less than 1% risk of post-operative mortality at 30, 60, and 90 days post-treatment, rates that are highly favorable not only in comparison to their counterparts undergoing surgery but also to other patients undergoing SBRT.

Our findings corroborate those of prior investigations into post-treatment mortality. The NCDB has previously been analyzed to demonstrate greater early mortality for surgically-treated patients versus those undergoing SBRT,[18] while among surgery patients, a recent analysis of the Society of Thoracic Surgeons database demonstrated that patients receiving minimally-invasive resections experience less 30-day mortality and major morbidity than those undergoing thoracotomies.[19] Our findings are consistent with these observations.

This analysis advances our understanding of post-treatment mortality with two novel findings. First, to our knowledge no previous studies have compared post-treatment mortality between patients undergoing minimally-invasive surgery and those undergoing SBRT. Despite the reduction in mortality risk with minimally-invasive techniques as compared to open resections, this reduced risk still (numerically but not statistically significantly) exceeds that following SBRT at all time points when adjusting for imbalances. The persistent excess risk suggests that minimally-invasive approaches such as VATS can decrease, but not eliminate, the incidence of cardiopulmonary events following surgery that are thought to contribute to post-treatment mortality.[20,21]

Second, our study is the first to assess the impact of operability status on post-treatment mortality in early-stage NSCLC patients treated with SBRT. While multiple prior analyses have identified superior survival among operable versus inoperable patients,[9–11] these earlier studies have focused on long-term survival outcomes rather than post-treatment mortality. As a result, the impact of operability has previously been characterized only in the context of a protracted time frame. In contrast, our analysis indicates that operability status actually becomes relevant far earlier, with the excess mortality for inoperable versus operable SBRT patients exceeding an absolute difference of 0.3% by 30 days, 1.1% by 60 days, and 2.2% by 90 days post-treatment. The manifestation of these differences within three months of treatment reflects the considerable influence of operability status in patients undergoing SBRT.

This observed differential invites inquiry into the underlying cause. Multiple series have evaluated SBRT in patients deemed inoperable for a variety of reasons encompassing advanced age, high comorbidity burdens, and/or frailty. These patients experience no increased acute toxicity risk as compared to their younger, healthier, or less frail counterparts.[22–25] These findings, coupled with the negligible rates of post-treatment mortality reported in prospective trials of inoperable patients undergoing SBRT,[26–29] suggest that the observed mortality events in our study are unlikely to be treatment-related. Instead, the differential mortality risk we observed more likely reflects the fundamental differences

in these populations captured by operability. The decision of whether to offer surgery to a specific patient is complex and requires a comprehensive assessment encompassing multiple factors that influence perioperative risk, including performance status, comorbidities, cardiopulmonary function, and age.[19,20] Patients deemed operable versus inoperable exhibit fundamentally different risk profiles that can translate into widely different outcomes, even when undergoing the same treatment modality.

Our study highlights the role of operability as a confounding variable in non-randomized comparisons of surgery with SBRT in early-stage NSCLC. The persistent association of operability with mortality risk after adjustment for other factors associated with post-treatment mortality, chiefly age and comorbidity, illustrates both the insufficiency of these latter factors and the value of the surgeon's judgement in risk stratification.[30] The early mortality differential by operability among SBRT patients underscores the impact of non-cancer-related, non-treatment-related mortality events in patients deemed unfit for surgery that may confound comparisons with surgical patients. Comparative-effectiveness analyses juxtaposing outcomes following surgery versus SBRT that do not account for operability are therefore vulnerable to this source of bias and should be interpreted with caution.

Strengths of our analysis include minimal loss to follow-up with early post-treatment endpoints, a large study population, and the inclusion of patients treated across the same institutional pool and over the same recent time period. Our study complements the existing body of literature for early-stage NSCLC by providing real-world evidence with relevance to patients either ineligible for randomized trials or poorly-represented on them.[31] Our findings may improve shared-decision-making between lung cancer clinicians and patients, particularly those who are deemed operable. The rare incidence of post-treatment mortality we observed among operable SBRT patients may be especially relevant for patients who wish to minimize their near-term risk for mortality while still undergoing effective treatment for early-stage NSCLC.

Among the chief limitations of our study is the subjectivity inherent to operability. The complex calculus that underlies an individual patient's suitability for surgery can vary according to the surgeon's skill and experience, prevailing institutional practice patterns, and local availability of SBRT. Assigning a binary status (operable versus inoperable) to this multifaceted criterion oversimplifies what is in reality a continuous spectrum of perioperative risk. Nevertheless, the decision to offer surgical resection to a patient constitutes a concrete and concise determination with direct implications for guideline-concordant therapy.[3–5]

A secondary limitation is the potential influence of systemic therapy on post-treatment mortality. Patients who underwent surgery and were pathologically upstaged may have received adjuvant chemotherapy, which may in turn have contributed to post-treatment mortality in this group, whereas SBRT patients typically do not receive adjuvant therapy.

Limitations inherent to NCDB are also applicable to our study. The use of nonrandomized data in comparative-effectiveness analysis introduces the potential for selection bias. In the present study, however, selection bias would be expected to favor surgical patients over

SBRT patients, who were either deemed unfit for surgery or may have elected non-surgical therapy due to perceived risk for surgical morbidity. It is therefore noteworthy that both SBRT groups experienced better short-term outcomes despite this potential for selection bias. Other limitations of the NCDB include the lack of data regarding disease control, cause of death, treatment toxicity, or quality of life, which are integral to shared decision-making for early-stage NSCLC.

Conclusion

In conclusion, operability status is strongly associated with post-treatment mortality among patients undergoing SBRT for early-stage NSCLC, with operable patients experiencing exceptionally low mortality risk within 90 days of treatment. These findings illustrate the profound influence of confounding by indication in non-randomized comparisons of surgical versus nonsurgical treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

Funding Sources

This work was supported in part by the Biostatistics and Bioinformatics Shared Resource of Winship Cancer Institute of Emory University and the National Cancer Institute at the National Institutes of Health (P30CA138292). Acquisition of data, analysis, interpretation, writing, and submission were performed without involvement of funding sources.

References

1. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395–409. [PubMed: 21714641]
2. Lu T, Yang X, Huang Y, et al. Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades. Cancer Manag Res. 2019;11:943–953. [PubMed: 30718965]
3. Ettinger DS, Wood DE, Aggarwal C, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 1.2020. J Natl Compr Canc Netw. 2019;17(12):1464–1472. [PubMed: 31805526]
4. Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e278S–e313S. [PubMed: 23649443]
5. Videtic GM, Chang JY, Chetty IJ, et al. ACR appropriateness Criteria(R) early-stage non-small-cell lung cancer. Am J Clin Oncol. 2014;37(2):201–207. [PubMed: 25180631]
6. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol. 2015;16(6):630–637. [PubMed: 25981812]
7. Bosco JL, Silliman RA, Thwin SS, et al. A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. J Clin Epidemiol. 2010;63(1):64–74. [PubMed: 19457638]

8. Kyriacou DN, Lewis RJ. Confounding by Indication in Clinical Research. JAMA. 2016;316(17):1818–1819. [PubMed: 27802529]
9. Schonewolf CA, Heskel M, Doucette A, et al. Five-year Long-term Outcomes of Stereotactic Body Radiation Therapy for Operable Versus Medically Inoperable Stage I Non-small-cell Lung Cancer: Analysis by Operability, Fractionation Regimen, Tumor Size, and Tumor Location. Clin Lung Cancer. 2019;20(1):e63–e71. [PubMed: 30337269]
10. 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(7 Suppl 3):S94–100. [PubMed: 17603311]
11. Kann BH, Verma V, Stahl JM, et al. *Multi-institutional* analysis of stereotactic body radiation therapy for operable early-stage non-small cell lung carcinoma. Radiother Oncol. 2019;134:44–49. [PubMed: 31005223]
12. Liu J, Hui C, Ladbury C, et al. Improved Survival Outcomes in Medically Fit Patients With Early-Stage Non-Small-Cell Lung Cancer Undergoing Stereotactic Body Radiotherapy. Clin Lung Cancer. 2021.
13. McNeil BJ, Weichselbaum R, Pauker SG. Fallacy of the five-year survival in lung cancer. N Engl J Med. 1978;299(25):1397–1401. [PubMed: 714117]
14. Liu Y, Nickleach DC, Zhang C, Switchenko JM, Kowalski J. Carrying out streamlined routine data analyses with reports for observational studies: introduction to a series of generic SAS ((R)) macros. F1000Res. 2018;7:1955. [PubMed: 31231506]
15. Imbens GW. The Role of the Propensity Score in Estimating Dose-Response Functions. Biometrika. 2000;87:706–710.
16. Liu Y, Nickleach D, Lipscomb J. Propensity Score Matching for Multiple Treatment Comparisons in Observational Studies. Proceedings of the 59th World Statistics Congress; 2013; Hong Kong.
17. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28(25):3083–3107. [PubMed: 19757444]
18. Stokes WA, Bronsert MR, Meguid RA, et al. Post-Treatment Mortality After Surgery and Stereotactic Body Radiotherapy for Early-Stage Non-Small-Cell Lung Cancer. J Clin Oncol. 2018;36(7):642–651. [PubMed: 29346041]
19. Fernandez FG, Kosinski AS, Burfeind W, et al. The Society of Thoracic Surgeons Lung Cancer Resection Risk Model: Higher Quality Data and Superior Outcomes. Ann Thorac Surg. 2016;102(2):370–377. [PubMed: 27209606]
20. Eguchi T, Bains S, Lee MC, et al. Impact of Increasing Age on Cause-Specific Mortality and Morbidity in Patients With Stage I Non-Small-Cell Lung Cancer: A Competing Risks Analysis. J Clin Oncol. 2017;35(3):281–290. [PubMed: 28095268]
21. Altorki NK, Wang X, Wigle D, et al. Perioperative mortality and morbidity after sublobar versus lobar resection for early-stage non-small-cell lung cancer: post-hoc analysis of an international, randomised, phase 3 trial (CALGB/Alliance 140503). Lancet Respir Med. 2018;6(12):915–924. [PubMed: 30442588]
22. Franco I, Chen YH, Chipidza F, et al. Use of frailty to predict survival in elderly patients with early stage non-small-cell lung cancer treated with stereotactic body radiation therapy. J Geriatr Oncol. 2018;9(2):130–137. [PubMed: 28941581]
23. Turzer M, Brustugun OT, Waldeland E, Helland A. Stereotactic body radiation therapy is effective and safe in patients with early-stage non-small cell lung cancer with low performance status and severe comorbidity. Case Rep Oncol. 2011;4(1):25–34. [PubMed: 21526003]
24. Giuliani M, Hope A, Guckenberger M, et al. Stereotactic Body Radiation Therapy in Octo- and Nonagenarians for the Treatment of Early-Stage Lung Cancer. Int J Radiat Oncol Bio Phys. 2017;98(4):893–899. [PubMed: 28258901]
25. Henderson M, McGarry R, Yiannoutsos C, et al. Baseline pulmonary function as a predictor for survival and decline in pulmonary function over time in patients undergoing stereotactic body radiotherapy for the treatment of stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2008;72(2):404–409. [PubMed: 18394819]

26. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA. 2010;303(11):1070–1076. [PubMed: 20233825]

27. Videtic GM, Hu C, Singh AK, et al. A Randomized Phase 2 Study Comparing 2 Stereotactic Body Radiation Therapy Schedules for Medically Inoperable Patients With Stage I Peripheral Non-Small Cell Lung Cancer: NRG Oncology RTOG 0915 (NCCTG N0927). Int J Radiat Oncol Biol Phys. 2015;93(4):757–764. [PubMed: 26530743]

28. Singh AK, Gomez-Suescun JA, Stephans KL, et al. One Versus Three Fractions of Stereotactic Body Radiation Therapy for Peripheral Stage I to II Non-Small Cell Lung Cancer: A Randomized, Multi-Institution, Phase 2 Trial. Int J Radiat Oncol Biol Phys. 2019;105(4):752–759. [PubMed: 31445956]

29. Bezjak A, Paulus R, Gaspar LE, et al. Safety and Efficacy of a Five-Fraction Stereotactic Body Radiotherapy Schedule for Centrally Located Non-Small-Cell Lung Cancer: NRG Oncology/RTOG 0813 Trial. J Clin Oncol. 2019;37(15):1316–1325. [PubMed: 30943123]

30. Stokes WA, Rusthoven CG. Surgery vs. SBRT in retrospective analyses: confounding by operability is the elephant in the room. J Thorac Dis. 2018;10(Suppl 17):S2007–S2010. [PubMed: 30023105]

31. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-World Evidence - What Is It and What Can It Tell Us? N Engl J Med. 2016;375(23):2293–2297. [PubMed: 27959688]

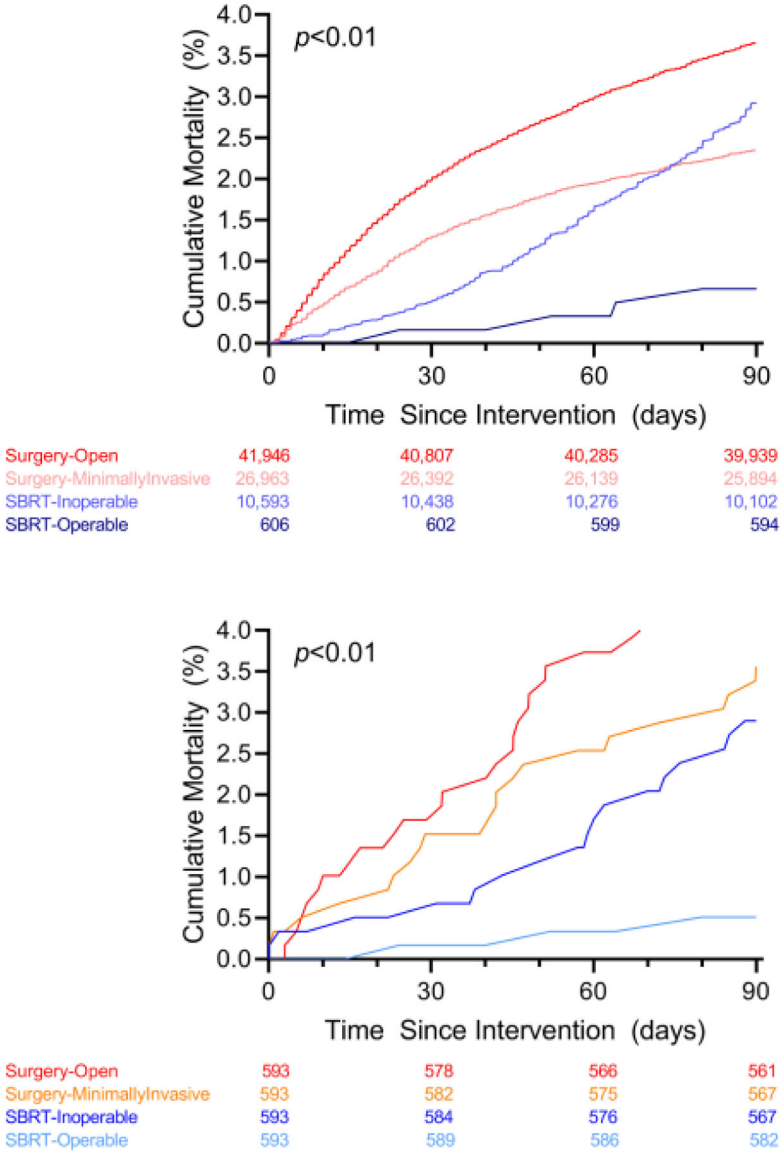

Figure 1.

Cumulative incidence of mortality by intervention and operability among **a**) entire cohort and **b**) propensity-score-matched cohort. SBRT, stereotactic body radiotherapy. Numbers beneath curves indicate numbers of patients at risk within in each group at each time point.

Table 1.

Descriptive Statistics Comparing Patients by Intervention & Operability

Covariate		SBRT				Surgery				*p* *
		Operable (n=606)		Inoperable (n=10,593)		Minimally Invasive (n=26,963)		Open (n=41,946)		
Age, years	**Median**	**76**		**75**		**68**		**68**		**<0.001**
		#	%	#	%	#	%	#	%	
Year	2010	79	13.0	1,502	14.2	3,607	13.4	9,651	23.0	<0.001
	2011	105	17.3	1,745	16.5	4,629	17.2	8,600	20.5	
	2012	117	19.3	2,062	19.5	52	20.4	8,092	19.3	
	2013	153	25.3	2,448	23.1	6,282	23.3	7,914	18.9	
	2014	152	25.1	2,836	26.8	6,943	25.8	7,689	18.3	
Sex	Male	253	41.7	4,654	43.9	11,328	42.0	19,337	46.1	<0.001
	Female	353	58.3	5,939	56.1	15,635	58.0	22,609	53.9	
Race	White	522	86.1	9,439	89.1	23,650	87.7	36,931	88.0	<0.001
	Black	69	11.4	915	8.6	2,159	8.0	3,597	8.6	
	Other	15	2.5	239	2.3	1,154	4.3	1,418	3.4	
Insurance	Not Insured/ Unknown	12	2.0	213	2.0	669	2.5	1,391	3.3	<0.001
	Private	67	11.1	1,242	11.7	8,233	30.5	12,866	30.7	
	Medicaid/Other Government	40	6.6	787	7.4	1,476	5.5	2,617	6.2	
	Medicare	487	80.4	8,351	78.8	16,585	61.5	25,072	59.8	
Income	< $30,000	73	12.0	1,424	13.4	2,896	10.7	5,683	13.5	<0.001
	$30,000 – $34,999	119	19.6	2,033	19.2	4,273	15.8	8,100	19.3	
	$35,000 – $45,999	158	26.1	3,091	29.2	7,218	26.8	11,930	28.4	
	$46,000 +	243	40.1	3,770	35.6	11,725	43.5	15,039	35.9	
	Unknown	13	2.1	275	2.6	851	3.2	1,194	2.8	
Facility Type	Non-Academic	398	65.7	6,306	59.5	14,851	55.6	28,719	69.3	<0.001
	Academic	208	34.3	4,287	40.5	11,872	44.4	12,740	30.7	
Comorbidity Score	0	382	63.0	5,570	52.6	13,100	48.6	20,314	48.4	<0.001
	1	149	24.6	2,985	28.2	9,837	36.5	15,090	36.0	
	2+	75	12.4	2,038	19.2	4,026	14.9	6,542	15.6	
Site	LLL	88	14.5	1,590	15.0	3,962	14.7	6,227	14.8	<0.001
	LUL	171	28.2	2,992	28.3	6,655	24.7	10,562	25.2	
	RLL	97	16.0	1,833	17.3	5,056	18.8	7,488	17.9	
	RML	35	5.8	468	4.4	1,691	6.3	2,535	6.0	
	RUL	206	34.0	3,457	32.6	8,979	33.3	13,576	32.4	
	Other	9	1.5	253	2.4	620	2.3	1,558	3.7	
T-Classification	T1 (nos)	58	9.6	1,128	10.7	3,231	12.0	5,539	13.2	<0.001
	T1a	208	34.3	3,698	34.9	10,890	40.4	13,438	32.0	

Covariate		SBRT				Surgery				*p* *
		Operable (n=606)		Inoperable (n=10,593)		Minimally Invasive (n=26,963)		Open (n=41,946)		
Age, years	**Median**	**76**		**75**		**68**		**68**		**<0.001**
		#	**%**	**#**	**%**	**#**	**%**	**#**	**%**	
	T1b	192	31.7	2,964	28.0	77	21.4	8,877	21.2	
	T2 (nos)	16	2.6	494	4.7	1,521	5.6	3,624	8.6	
	T2a	115	19.0	2,060	19.5	58	16.9	8,026	19.1	
	T2b	17	2.8	249	2.4	996	3.7	2,442	5.8	
Histology	Squamous Cell Carcinoma	189	31.2	3,917	37.0	6,182	22.9	11,392	27.2	<0.001
	Adenocarcinoma	329	54.3	4,879	46.1	16,707	62.0	23,881	56.9	
	Other	88	14.5	1,797	17.0	04	15.1	6,673	15.9	

*The parametric p-value is calculated by ANOVA for numerical covariates and χ^2-square test for categorical covariates.

Table 2.

Absolute Mortality Estimates by Intervention at Specified Time Points Post-Intervention, All Patients

		SBRT				Surgery				
Days Post-Treatment	**Outcome**	**Operable**		**Inoperable**		**Minimally-Invasive**		**Open**		***p*** *
		#	**%**	**#**	**%**	**#**	**%**	**#**	**%**	
30	Alive	602	99.3	10,438	98.5	26,392	97.9	40,807	97.3	<0.001
	Dead	1	**0.2**	54	**0.5**	351	**1.3**	842	**2.0**	
	Censored	3	0.5	101	1.0	220	0.8	297	0.7	
60	Alive	599	98.8	10,276	97.0	26,139	96.9	40,285	96.0	<0.001
	Died	2	**0.3**	170	**1.6**	526	**2.0**	1,255	**3.0**	
	Censored	5	0.8	147	1.4	298	1.1	406	1.0	
90	Alive	594	98.0	10,102	95.4	25,984	96.4	39,939	95.2	<0.001
	Died	4	**0.7**	306	**2.9**	634	**2.4**	1,535	**3.7**	
	Censored	8	1.3	185	1.7	345	1.3	472	1.1	

* The p-value is calculated by χ^2-square test.

Table 3.

Absolute Mortality Estimates by Intervention at Specified Time Points Post-Intervention, Propensity-Matched Cohort

Days Post-Treatment	Outcome	SBRT				Surgery				*p* *
		Operable		Inoperable		Minimally-Invasive		Open		
		#	%	#	%	#	%	#	%	
30	Alive	589	99.3	584	98.5	582	98.2	578	97.5	0.032
	Dead	1	**0.2**	3	**0.5**	9	**1.5**	11	**1.9**	
	Censored	3	0.5	6	1.0	2	0.3	4	0.7	
60	Alive	586	98.8	576	97.1	575	97.0	566	95.5	<0.001
	Died	2	**0.3**	9	**1.5**	15	**2.5**	23	**3.9**	
	Censored	5	0.8	8	1.4	3	0.5	4	0.7	
90	Alive	582	98.2	567	95.6	567	95.6	561	94.6	0.002
	Died	3	**0.5**	17	**2.9**	21	**3.5**	27	**4.6**	
	Censored	8	1.4	9	1.5	5	0.8	5	0.8	

*The p-value is calculated by χ^2-square test.