Comparative effectiveness of stereotactic body radiation therapy versus surgery for stage I lung cancer in otherwise healthy patients: An instrumental variable analysis

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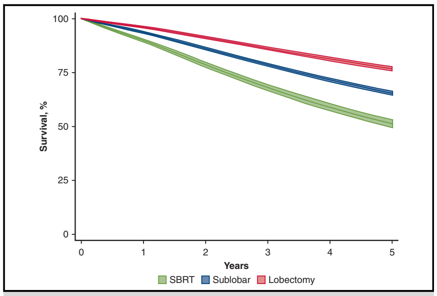
ABSTRACT

Objectives: Stereotactic body radiation therapy (SBRT) is an established primary treatment modality in patients with lung cancer who have multiple comorbidities and/or advanced-stage disease. However, its role in otherwise healthy patients with stage I lung cancer is unclear. In this context, we compared the effectiveness of SBRT versus surgery on overall survival using a national database.

Methods: We identified all patient with clinical stage I non–small cell lung cancer from the National Cancer Database from 2004 to 2016. We defined otherwise healthy patients as those with a Charlson-Deyo comorbidity index of 0 and whose treatment plan included options for either SBRT or surgery. We further excluded patients who received SBRT due to a contraindication to surgery. We first used propensity score matching and Cox proportional hazard models to identify associations. Next, we fit 2-stage residual inclusion models using an instrumental variables approach to estimate the effects of SBRT versus surgery on long-term survival. We used the hospital SBRT utilization rate as the instrument.

Results: Of 25,963 patients meeting all inclusion/exclusion criteria, 5465 (21%) were treated with SBRT. On both Cox proportional hazards modeling and propensity-score matched Kaplan-Meier analysis, surgical resection was associated with improved survival relative to SBRT. In the instrumental-variable–adjusted model, SBRT remained associated with decreased survival (hazard ratio, 2.64; $P < .001$). Both lobectomy (hazard ratio, 0.17) and sublobar resections (hazard ratio, 0.28) were associated with improved overall survival compared with SBRT ($P < .001$).

Conclusions: In otherwise healthy patients with stage I NSCLC, surgical resection is associated with a survival benefit compared with SBRT. This is true for both lobar and sublobar resections. (JTCVS Open 2022;9:249-61)



Survival curve comparing overall survival after adjusting for the instrument.

CENTRAL MESSAGE

In otherwise healthy patients with stage I NSCLC, surgical resection is associated with a survival benefit compared with SBRT. This is true for both lobar and sublobar resections.

PERSPECTIVE

The comparative effectiveness of SBRT as the primary treatment modality in operable patients with stage I NSCLC is unknown. Using causal inference research design, we demonstrate that surgical resection, regardless of extent, in otherwise healthy patients with stage I NSCLC is associated with better survival. The findings have important implications for shared decision making.

See Commentaries on pages 262 and 264.

Lung cancer causes approximately 150,00 deaths each year in the United States alone and is the leading cause of cancer-related mortality.[1] Expert consensus panels, including the National Comprehensive Cancer Network, recommend margin-negative surgical resection with appropriate lymph node assessment as the optimal treatment.[2,3] However,

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Abbreviations and Acronyms

CoC = Commission on Cancer
NCDB = National Cancer Database
NSCLC = non–small cell lung cancer
SBRT = stereotactic body radiation therapy

some patients are not operative candidates or elect not to undergo surgery. Stereotactic body radiation therapy (SBRT) has emerged as a safe and effective treatment modality for patients unwilling or unable to undergo surgical resection.[4] SBRT is associated with lower 30- and 90-day mortality than resection,[5] while still providing high rates of tumor control.[6] However, the comparative effectiveness of SBRT relative to resection for patients who are surgical candidates remains unclear.

Three prospective randomized trials attempted to compare SBRT with resection in patients with early-stage non–small cell lung cancer (NSCLC), but they did not have sufficient patient recruitment (ie, American College of Surgeon Oncology Group Z4099, Stereotactic Ablative Radiotherapy in Stage I Non-small Cell Lung Cancer Patients Who Can Undergo Lobectomy, and Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage (IA) Lung Cancer).[7-9] The latter 2 studies pooled their results and conducted a secondary analysis that suggested SBRT was associated with improved survival compared with surgery.[10] However, this analysis has received multiple criticisms, including a final sample size of only 58 patients.[11] Since the publication of this study by Chang and colleagues[10] and resultant criticisms, numerous retrospective studies have attempted to compare outcomes between SBRT and resection for early-stage NSCLC.[5,12-15] Overall, they suggest improved survival from surgery relative to SBRT. However, those studies are limited by selection bias, and it is difficult to know if the survival benefit identified is due to a true benefit of surgery over SBRT or that patients selected for surgery were simply healthier than those electing to undergo SBRT. One study by Rosen and colleagues[15] did include a propensity-score matched subgroup analysis of patients who refused surgery and instead opted to undergo SBRT, and demonstrated a similar survival benefit from lobectomy. However, the results are limited only to patients undergoing lobectomy. We elected to build on that by including both lobar and sublobar resections and exploring the analysis with a different methodological design.

In this context, we performed an instrumental variable analysis using the National Cancer Database (NCDB) (National Cancer Data Base Participant User File Data Dictionary. National Cancer Database 2016; American College of Surgeons) to compare long-term survival among otherwise healthy patients treated with SBRT versus surgery. The patients included in our cohort could theoretically undergo either treatment. In the absence of robust data from a randomized trial, instrumental variable analysis is a useful technique for estimating treatment effects using observational data while accounting for unmeasured confounders. Instrumental variable analysis is an econometric method in which naturally occurring variation within observational data are leveraged to balance measured and unmeasured confounding among treatment groups.[16] Using this method, selection bias is further reduced by taking into account institution-related treatment patterns that can directly affect which treatment is chosen, which in turn, allows us to infer the effect of the treatment on outcomes in a hypothetical patient who could undergo either modality. This statistical method has been used previously in the medical literature.[17-19] By applying this technique, we can clarify the comparative effectiveness of SBRT and surgery in the treatment of healthy patients with early-stage lung cancer.

METHODS

Data Source

This study was reviewed and deemed exempt by our institution's institutional review board (#214299 on November 6, 2020). The NCDB is a nationally representative oncology registry administered jointly by the American Cancer Society and the American College of Surgeons. The database captures an estimated 70% of all newly diagnosed malignancies in the United States and contains records on an estimated 34 million patients from approximately 1500 hospitals accredited by the Commission on Cancer (CoC).

Patient Population

We queried the NCDB for records of adult patients diagnosed with clinical stage I (cT1 N0) NSCLC from 2004 to 2016. We only included patients with a Charlson-Deyo comorbidity index of 0, patients who were offered surgery but declined and opted for SBRT instead, patients in whom lung cancer was their first and only cancer diagnosis, and patients with clinical T stage of T1 and tumor size <3 cm. We excluded patients whose reason for receiving SBRT was due to a contraindication to surgery. We also excluded patients undergoing pneumonectomy. As such, the cohort comprises otherwise healthy patients, without comorbidity nor contraindication to surgery, and whose treatment plan included multiple options and they elected to receive either SBRT or surgical resection as defined in the NCDB data dictionary.[20]

Variable Coding

Our main outcome of interest was overall survival, which was defined as the time from diagnosis to death due to any cause. Other variables included in our analyses were age, race, insurance status, patient income, patient education, disease laterality, year of diagnosis, histology, facility type, facility location, tumor size, and extent of resection. Age was categorized as age younger than 50 years, age 50 to 70 years, and age older than 70 years. Race was defined as White, Black, other, or unknown. Insurance status was classified as private, government, uninsured, or unknown. Patient income was coded as the median income of the zip code in which that patient resided which was then further divided into quartiles. Patient educational attainment was coded based on the proportion of individuals in that patient's zip code without a high school diploma. Year of diagnosis was categorized as 2004-2008, 2009-2012, and 2013-2016. Facility location was classified based on geographic region. Histology was classified as adenocarcinoma, squamous cell carcinoma, or other. Tumor size was categorized as <1 cm, 1 to 2 cm, or 2 to 3 cm. Extent of resection was categorized as sublobar resection (wedge resection or segmentectomy) or lobectomy.

Statistical Analysis

We used Student *t* tests and χ^2 statistics for univariate comparisons as appropriate for patients receiving SBRT versus those undergoing resection. To minimize confounding by indication, we first used propensity score matching. Patients receiving SBRT were then 1:1 propensity-score matched to patients undergoing surgical resection using the nearest neighbor method without replacement. Propensity scores for each patient were generated from a multivariable logistic regression adjusting for age, gender, race, insurance provider, patient income, patient education, year of diagnosis, tumor size, tumor laterality, tumor histology, treating facility type, and facility location. The quality of the match was assessed by comparing the standardized bias between the groups for each variable included in the match, with a cutoff <0.10 used to indicate no difference. The Kaplan-Meier method was used to compare survival between matched cohorts.

The instrumental variable method addresses both measured and unmeasured confounding that may not be captured in our multivariable or propensity matched models. It is a method for estimating causal effects in observational data by leveraging random variation in 1 variable (the instrument: hospital SBRT utilization rate in the study period) that affects the probability of treatment for the patients. In this case, the probability of SBRT is higher if the patient happens to go to a hospital that has utilized SBRT more frequently. The random variation in the hospital's SBRT use only affects a patient's survival through his or her choice of clinical treatment.

In this analysis, we use a 2-stage residual inclusion approach.[21] During the first stage, we fit a multivariable logistic regression model to evaluate the association between the instrument and SBRT. An instrument is considered strong if the F statistic is > 10 (in this study the minimum eigenvalue F statistic = 4928.04, indicating strong correlation between the instrument and the treatment). The residuals were then obtained using postestimation prediction and were included in our second stage multivariable Cox model to estimate the average treatment effect. We then used the Durbin test for endogeneity to confirm that the instrument is exogenous to other variables.

We then used Cox proportional hazards modeling to identify factors associated with overall survival. This residual inclusion model adjusted for treatment modality (SBRT vs resection), age, gender, race, insurance provider, patient income quartile, patient education quartile, tumor size, and year of diagnosis. Robust standard errors were used to account for clustering.

Statistical analyses were performed using R version 3.6.0 (R Foundation for Statistical Computing) and Stata version 13.1SE (Stata Corp). All tests were 2-sided using a P value < .05. CIs are reported to a 95% confidence level.

RESULTS

Patient Population

Overall, 25,963 patients met all inclusion criteria. Five thousand four hundred sixty-five (21%) were treated with SBRT, whereas 20,498 (79%) underwent surgical resection. Of the patients undergoing surgery, 15,822 (77.2%) underwent lobectomy, and 4676 (22.8%) underwent sublobar resection. For patients undergoing surgical resection, the median number of lymph nodes examined was 6 with an interquartile range between 3 and 11. Of the surgical cohort, 11 patients were found to have lymph node metastases on final pathology. Five patients were upstaged to N1 disease, and 6 were upstaged to N2 disease.

Univariate Comparisons

Table 1 displays the univariate unadjusted comparison of demographic characteristics, treatment, and histopathologic characteristics for patients undergoing surgical resection versus SBRT. Patients receiving SBRT were older (74.9 ± 9.1 years vs 66.8 ± 10.2 years; P < .001), were more likely to have squamous histology (30.9% vs 18.2%; P < .001), and were less likely to have private insurance (13.2% vs 34.3%; P < .001).

Cox Proportional Hazards Analysis

On Cox proportional hazards analysis (Table 2), age older than 70 years (hazard ratio [HR], 2.32; 95% CI, 2.01-2.69; P < .001), government insurance (HR, 1.41; 95% CI, 1.33-1.49; P < .001), tumor size 2 to 3 cm (HR, 1.28; 95% CI, 1.20-1.37; P < .001), and squamous histology (HR, 1.12; 95% CI, 1.01-1.25; P = .03)were associated with worse survival. Factors associated with increased survival included female gender (HR, 0.72; 95% CI, 0.69-0.75; P < .001), increased patient income (>75th percentile HR, 0.78; 95% CI, 0.72-0.85; P < .001), later diagnosis year (2012-2016 HR, 0.69; 95% CI, 0.65-0.73; P < .001), treatment at an academic facility (HR, 0.69; 95% CI, 0.64-0.75; P < .001), and treatment with surgical resection (HR, 0.35; 95% CI, 0.33-0.36; P < .001).

Propensity-Score Matched Survival Analysis

Five thousand three hundred ninety-two patients receiving SBRT (out of 5465 total) were 1:1 propensity-score matched with 5,392 patients undergoing surgical resection. After matching, there were no differences between cohorts as measured by standardized bias (Table 3). On Kaplan-Meier analysis of matched cohorts, patients undergoing surgical resection demonstrated median overall survival that was 57.5 months longer than patients receiving SBRT alone (98.76 ± 0.01 months vs 41.26 ± 0.007 months; P < .001). Figure 1 shows the overall survival on Kaplan-Meier analysis of the propensity-score matched cohort.

Instrumental Variable Analysis

To validate our instrument, we first set out to show that it was correlated with the treatment variables but not our outcome of instrument. As expected, the instrument of facility SBRT rate significantly predicted the likelihood of receiving SBRT (F statistic = 4928.04), yet it was not associated with survival on the residual inclusion Cox model (residual adjusted HR = 1.00; P = .999), and it was indeed an exogenous variable. These results support the validity of the instrument for the analysis. Improved balance is noted in Table E1. Table 4 shows the instrumental–variable-adjusted Cox model. As mentioned above, the instrument was not associated with overall survival. Surgical resections of all extents were associated with better survival than SBRT

TABLE 1. Univariate comparison of patient cohorts before propensity score matching

Characteristic	Surgery	Radiation therapy	*P* value
No. of patients	20,498	5465	
Age (%)			<.001
<50 y	1318 (6.4)	37 (0.7)	
50-70 y	11,235 (54.8)	1609 (29.4)	
>70 y	7945 (38.8)	3819 (69.9)	
Female sex (%)	12,460 (60.8)	3169 (58.0)	<.001
Race (%)			<.001
White	17,781 (86.7)	4831 (88.4)	
Black	1653 (8.1)	487 (8.9)	
Other	909 (4.4)	108 (2.0)	
Unknown	155 (0.8)	39 (0.7)	
Insurance status (%)			<.001
Private insurance	7039 (34.3)	720 (13.2)	
Government insurance	12,724 (62.1)	4544 (83.1)	
Uninsured	394 (1.9)	48 (0.9)	
Unknown	341 (1.7)	153 (2.8)	
Income quartile (%)			<.001
<25	3452 (17.0)	1143 (21.2)	
25-50	4249 (21.0)	1344 (24.9)	
50-75	4636 (22.9)	1339 (24.8)	
>75	7926 (39.1)	1566 (29.0)	
No high school diploma (%)			<.001
≥17.6	3779 (18.6)	1081 (20.0)	
10.9-17.5	5248 (25.9)	1630 (30.2)	
6.3-10.8	5804 (28.6)	1516 (28.1)	
<6.3	5466 (26.9)	1176 (21.8)	
Laterality (%)			<.001
Right	12,385 (60.4)	3078 (56.3)	
Left	8103 (39.5)	2379 (43.5)	
Other	6 (0.0)	2 (0.0)	
Unknown	4 (0.0)	6 (0.1)	
Diagnosis y (%)			<.001
2004-2008	4502 (22.0)	974 (17.8)	
2009-2012	8146 (39.7)	1947 (35.6)	
2012-2016	7850 (38.3)	2544 (46.6)	
Histology (%)			<.001
Adenocarcinoma	15,171 (74.0)	2676 (49.0)	
Squamous cell carcinoma	3727 (18.2)	1686 (30.9)	
Other	1600 (7.8)	1103 (20.2)	
Facility type (%)			<.001
Community program	1457 (7.1)	315 (5.8)	
Comprehensive community program	8729 (42.8)	2298 (42.0)	
Academic/research program	7833 (38.4)	2111 (38.6)	
Integrated network program	2371 (11.6)	741 (13.6)	
Facility location (%)			<.001
New England	1571 (7.7)	303 (5.5)	
Middle Atlantic	3691 (18.1)	725 (13.3)	
South Atlantic	4635 (22.7)	1416 (25.9)	
East North Central	3211 (15.7)	974 (17.8)	
East South Central	1413 (6.9)	391 (7.2)	
West North Central	1547 (7.6)	486 (8.9)	
West South Central	1235 (6.1)	453 (8.3)	
Mountain	807 (4.0)	223 (4.1)	
Pacific	2280 (11.2)	494 (9.0)	
Tumor size (%)			<.001
<1 cm	1336 (6.5)	162 (3.0)	
1-2 cm	12,705 (62.0)	3018 (55.2)	
2-3 cm	6457 (31.5)	2285 (41.8)	
Surgery type (%)			<.001
Wedge/segmentectomy	4676 (22.8)	0 (0.0)	
Lobectomy	15,822 (77.2)	0 (0.0)	

(lobectomy HR, 0.32; sublobar resection HR, 0.52; and pneumonectomy HR, 0.63).

Figure 2 shows the instrumental–variable-adjusted overall survival. Any surgical resection is associated with improved survival when compared with SBRT, even after adjusting for the instrument.

DISCUSSION

In this nationally representative study utilizing a causal inference research design to address the comparative effectiveness of SBRT versus surgery in otherwise healthy stage I lung cancer we found that surgical resection is associated with better survival compared with SBRT and that even a sublobar resection was associated with improved survival compared with SBRT. These findings have important implications for optimal shared decision making when considering treatment options for early-stage lung cancer (Figure 3).

Prior studies have been limited in their ability to assess the relative value of SBRT compared with surgical resection in early-stage NSCLC. Three prospective trials failed to enroll enough patients. A post hoc analysis of pooled patients from 2 of the trials suggested SBRT was associated with improved survival, but this study only contained 58 patients, approximately 3% of the projected combined sample size of the 3 trials.[10,11] In light of the lack of high-quality level-I evidence, multiple retrospective analyses have attempted to answer this question as well. The largest of these contained 1359 patients undergoing SBRT and propensity matched them to 136,784 patients undergoing resection.[12] They successfully matched 1315 pairs and ultimately identified a survival benefit from surgery compared with SBRT. Other studies included smaller numbers of patients

TABLE 2. Cox proportional hazards analysis identifying factors associated with increased risk of death

Characteristic	Hazard ratio	Lower	Higher	*P* value
Treatment = surgery (ref = SBRT)	0.35	0.33	0.36	<.001
Age (ref = < 50 y)				
50-70 y	1.50	1.30	1.73	<.001
>70 y	2.32	2.01	2.69	<.001
Female sex (ref = male sex)	0.72	0.69	0.75	<.001
Race (ref = White)				
Black	0.95	0.88	1.03	.20
Other	0.72	0.62	0.83	<.001
Unknown	0.81	0.62	1.05	.10
Insurance status (ref = private insurance)				
Government insurance	1.41	1.33	1.49	<.001
Uninsured	1.17	0.97	1.42	.11
Unknown	1.21	1.04	1.42	.02
Income quartile (ref = <25%)				
25%-50%	0.90	0.84	0.96	<.001
50%-75%	0.84	0.79	0.91	<.001
>75%	0.78	0.72	0.85	<.001
No high school diploma (ref = >17.6%)				
10.9%-17.5%	1.01	0.94	1.07	.86
6.3%-10.8%	1.00	0.93	1.07	.90
<6.3%	0.93	0.85	1.01	.08
Histology (ref = adenocarcinoma)				
Squamous cell carcinoma	1.12	1.01	1.25	.03
Other	1.29	1.16	1.43	<.001
Tumor size (ref = <1 cm)				
1-2 cm	1.46	1.39	1.53	<.001
2-3 cm	1.28	1.20	1.37	<.001
Laterality (ref = right)				
Left	1.01	0.97	1.06	.51
Other	1.83	0.69	4.89	.23
Unknown	1.03	0.54	1.99	.92
Year of diagnosis (ref = 2004-2008)				
2009-2012	0.87	0.83	0.92	<.001
2012-2016	0.69	0.65	0.73	<.001
Facility type (ref = community program)				
Comprehensive community program	0.84	0.78	0.91	<.001
Academic/research program	0.69	0.64	0.75	<.001
Integrated network program	0.79	0.72	0.87	<.001
Facility location (ref = New England)				
Middle Atlantic	1.03	0.93	1.15	.53
South Atlantic	1.13	1.02	1.24	.02
East North Central	1.16	1.05	1.28	<.001
East South Central	1.24	1.10	1.39	<.001
West North Central	1.15	1.03	1.29	.01
West South Central	1.13	1.00	1.27	.04
Mountain	1.05	0.92	1.20	.48
Pacific	1.06	0.95	1.18	.32

(Continued)

TABLE 2. Continued

SBRT, Stereotactic body radiation therapy.

receiving SBRT and identified similar survival benefits from resection.[13-15] In contrast, 1 study comparing 8216 patients receiving SBRT to 76,623 patients undergoing resection identified increases in both 30- and 90-day mortality from resection relative to SBRT.[5] As retrospective analyses, these prior studies all suffer from the potential selection bias and confounding variables inherent to such study design.

In the study presented here, we sought to clarify this issue by performing an instrumental variable analysis based on a large nationally representative cohort of patients with lung cancer whose treatment reflects contemporary practice patterns and surgical techniques. With this approach, we found that for patients with early-stage lung cancer, surgical resection (both lobar and sublobar) was associated with better overall survival. Accordingly, our findings support surgery, regardless of extent, as the preferred treatment option for the expanding pool of patients with stage I lung cancer detected on lung cancer screening.

The degree to which an instrumental variable analysis alleviates measured and unmeasured confounding depends on the appropriate selection of an instrument that induces meaningful variation in the treatment without independently influencing the outcome of interest. The hospital rate at which a certain treatment is given has been previously used in the literature as an instrument and has face validity. It provides an idea of the practice patterns at these CoC centers. Consistent with previous work,[17-19] this instrument met these criteria convincingly in our analysis. As such, our methods should effectively balance both measured and unmeasured confounding in this cohort. In addition, strictly limiting our inclusion and exclusion criteria creates a group of patients who could truly receive either treatment, but due to practice patterns or patient preference, 1 approach was favored over the other.

The main issue at hand is how to counsel patients with clinical, early-stage lung cancer who are potentially fit for an operation. The results of this observational study presented herein build upon current evidence that surgical

TABLE 3. Univariate comparison of patient cohorts after propensity score matching

Characteristic	Surgery	Radiation therapy	*P* value	Standardized mean difference
No. of patients	5392	5392		
Age (%)			.534	0.02
<50 y	28 (0.5)	37 (0.7)		
50-70 y	1586 (29.4)	1582 (29.3)		
>70 y	3778 (70.1)	3773 (70.0)		
Female sex (%)	3169 (58.8)	3138 (58.2)	.558	0.01
Race (%)			.861	0.02
White	4793 (88.9)	4768 (88.4)		
Black	456 (8.5)	478 (8.9)		
Other	102 (1.9)	107 (2.0)		
Unknown	41 (0.8)	39 (0.7)		
Insurance status (%)			.009	0.07
Private insurance	601 (11.1)	708 (13.1)		
Government insurance	4613 (85.6)	4486 (83.2)		
Uninsured	43 (0.8)	47 (0.9)		
Unknown	135 (2.5)	151 (2.8)		
Income quartile (%)			.957	0.01
<25%	1143 (21.2)	1143 (21.2)		
25%-50%	1324 (24.6)	1344 (24.9)		
50%-75%	1360 (25.2)	1339 (24.8)		
>75%	1565 (29.0)	1566 (29.0)		
No high school diploma (%)			.866	0.02
≥17.6%	1099 (20.4)	1076 (20.0)		
10.9%-17.5%	1596 (29.6)	1630 (30.2)		
6.3%-10.8%	1534 (28.4)	1516 (28.1)		
<6.3%	1163 (21.6)	1170 (21.7)		
Laterality (%)			.763	0.02
Right	3055 (56.7)	3033 (56.2)		
Left	2332 (43.2)	2351 (43.6)		
Other	2 (0.0)	2 (0.0)		
Unknown	3 (0.1)	6 (0.1)		
Diagnosis y (%)			.630	0.02
2004-2008	928 (17.2)	966 (17.9)		
2009-2012	1930 (33.0)	1913 (35.5)		
2012-2016	2534 (47.0)	2513 (46.6)		
Histology (%)			<.001	0.10
Adenocarcinoma	2753 (51.1)	2635 (48.9)		
Squamous cell carcinoma	1779 (33.0)	1673 (31.0)		
Other	860 (15.9)	1084 (20.1)		
Facility type (%)			.673	0.02
Community program	315 (5.8)	311 (5.8)		
Comprehensive community program	2330 (43.2)	2276 (42.2)		
Academic/research program	2016 (37.4)	2076 (38.5)		
Integrated network program	731 (13.6)	729 (13.5)		
Facility location (%)			.894	0.04
New England	308 (5.7)	301 (5.6)		
Middle Atlantic	763 (14.2)	719 (13.3)		
South Atlantic	1363 (25.3)	1392 (25.8)		
East North Central	957 (17.7)	963 (17.9)		
East South Central	396 (7.3)	387 (7.2)		
West North Central	456 (8.5)	483 (9.0)		
West South Central	424 (7.9)	446 (8.3)		

(Continued)

TABLE 3. Continued

Characteristic	Surgery	Radiation therapy	*P* value	Standardized mean difference
Mountain	220 (4.1)	215 (4.0)		
Pacific	505 (9.4)	486 (9.0)		
Tumor size (%)			.611	0.02
< 1 cm	150 (2.8)	162 (3.0)		
1-2 cm	3019 (56.0)	2976 (55.2)		
2-3 cm	2223 (41.2)	2254 (41.8)		

resection (regardless of extent) remains the standard of care and the primary treatment modality in patients with stage I lung cancer. One key finding in our study is that even a sublobar resection was associated with improved survival compared with SBRT. Although lobectomy is the surgical gold standard, we found that a lesser resection is still associated with improved outcomes compared with SBRT. In other words, when patients are counseled, surgeons should use their judgment before shying away from all surgical options. Ultimately, a patient's involvement in shared decision making is paramount. Although we observed improved survival with resection, we do not have data on quality of life following treatment with either modality. Ongoing clinical trials will soon provide a more comprehensive answer to these questions. Until then, the results presented here favor surgery for those patients who can tolerate it.

This study has several limitations. Because the sample includes only patients treated at CoC centers, our results may not be generalizable. Nevertheless, this database represents 70% of all cancer diagnoses in the United States and has been used extensively in the literature. Second, the NCDB does not contain data on disease recurrence. Because of this, we are unable to draw conclusions on disease-free survival. However, our selected patient population is otherwise healthy and only diagnosed with lung cancer; one would assume that the overall survival and disease-free survival in this cohort would be rather similar. Third, the NCDB does not collect data on pulmonary function. To ameliorate this, we included all extents of resection and excluded patients who underwent SBRT due to a contraindication to surgery. The NCDB also lacks more granular pathological data in patients not undergoing surgery. For example, tumor grade was only documented in 41% of the SBRT group. Of those, 56% had high grade compared with 77% in the surgical cohort. We also were unable to control for the histologic grade in our analyses.

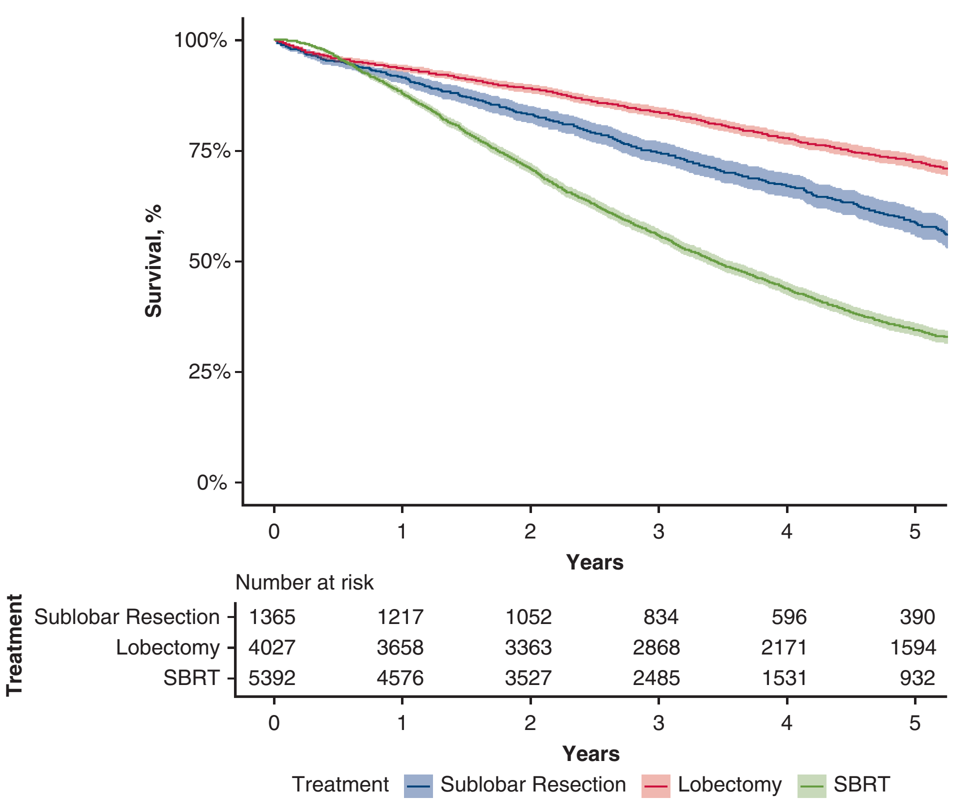


FIGURE 1. Kaplan-Meier survival curve comparing overall survival between propensity-matched cohorts. Shading indicates 95% CI. *SBRT*, Stereotactic body radiation therapy.

TABLE 4. Instrumental variable-adjusted Cox proportional hazards analysis identifying factors associated with increased risk of death

Characteristic	Hazard ratio	Lower	Higher	*P* value
Residual inclusion	1.00	0.88	1.13	.995
Age	1.03	1.03	1.03	<.001
Male sex (ref = female sex)	1.40	1.34	1.45	<.001
Race = White (ref = non-White)	1.17	1.09	1.25	<.001
Treatment modality (ref = SBRT)				
Sublobar	0.51	0.4	0.55	<.001
Lobectomy	0.32	0.31	0.34	<.001
Tumor size (ref = 1-2 cm)				
< 1 cm	0.82	0.74	0.91	<.001
2-3 cm	1.17	1.12	1.23	<.001
Insurance status (ref = private insurance)				
Government insurance	1.28	1.21	1.36	<.001
Uninsured	1.22	1.02	1.47	.033
Unknown	1.12	0.96	1.30	.165
Histology (ref = adenocarcinoma)				
Squamous cell carcinoma	1.46	1.40	1.54	<.001
Other	1.25	1.17	1.33	<.001
Year of diagnosis (ref = 2004-2008)				
2009-2012	0.86	0.82	0.90	<.001
2012-2016	0.68	0.64	0.72	<.001
Patient education (ref = <20%)				
20%-40%	1.02	0.96	1.09	.484
40%-60%	1.02	0.95	1.09	.586
60%-80%	0.94	0.87	1.02	.151
80%-100%	0.57	0.36	0.90	.016
Patient income (ref = <20%)				
20%-40%	0.87	0.82	0.93	<.001
40%-60%	0.81	0.75	0.87	<.001
60%-80%	0.69	0.64	0.75	<.001
80%-100%	1.37	0.91	2.07	.135

SBRT, Stereotactic body radiation therapy.

Although surgical resections typically provide adequate tissue for staging and histopathologic analyses, 59% of patients receiving SBRT had missing or unknown values for histologic grade in our cohort, which precluded us from including it in our modeling. Additionally, the NCDB does not contain information on specific staging procedures that patients might have undergone. It is possible that some patients receiving SBRT might not have been adequately staged. Although we were able to report the number of patients undergoing resection who were upstaged following final lymph node pathology, these data are not available for patients undergoing SBRT. Patients in the SBRT group may be understaged with, for example, occult N2 disease coded as N0 if they did not undergo a more invasive staging procedure, such as endobronchial ultrasound, before receiving SBRT. The NCDB also does not capture data on postoperative complications or health care-related quality of life. Without these data, we are unable to comment on the quality of life after either modality. The survival advantage noted with surgery may not be associated with improved quality of life, particularly should surgical complications arise. This particular question will be addressed in the Veterans Affairs Lung Cancer Surgery or Stereotactic Radiotherapy Trial (NCT02984761),[22] the results of which are expected to be available in 2027. Finally, results from instrumental variable analyses are applicable to hypothetical marginal patients who are candidates for either treatment approach. Although the NCDB does not provide pertinent information that can affect treatment decisions, our strict inclusion and exclusion criteria simulate such conditions, and the findings have face validity. Notwithstanding these limitations, we believe our results are timely and are relevant to the readership because they provide additional context surrounding clinical decision making for patients presenting with resectable NSCLC.

CONCLUSIONS

In otherwise healthy patients presenting with stage I NSCLC, surgical resection is associated with a survival

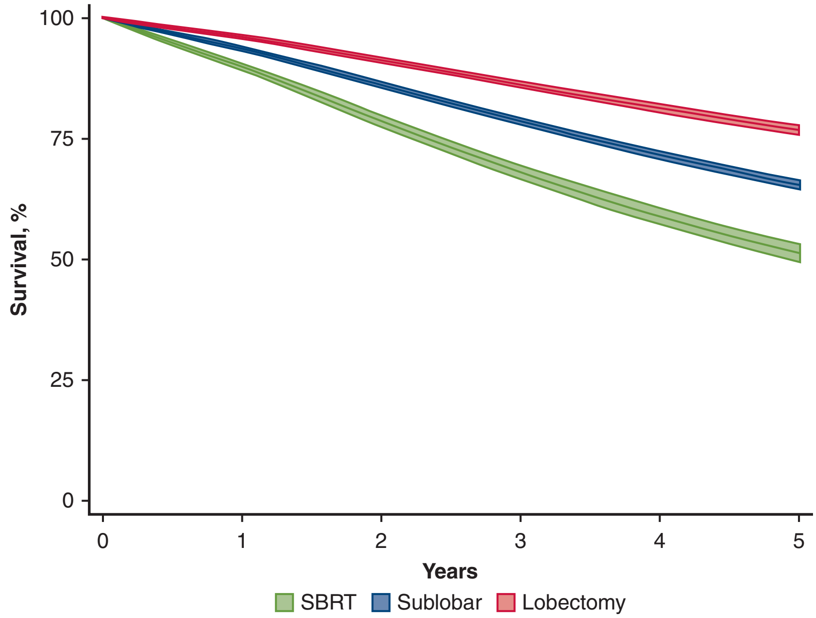


FIGURE 2. Instrumental-variable–adjusted survival curve comparing overall survival after adjusting for the instrument. *Shading* indicates 95% CI.

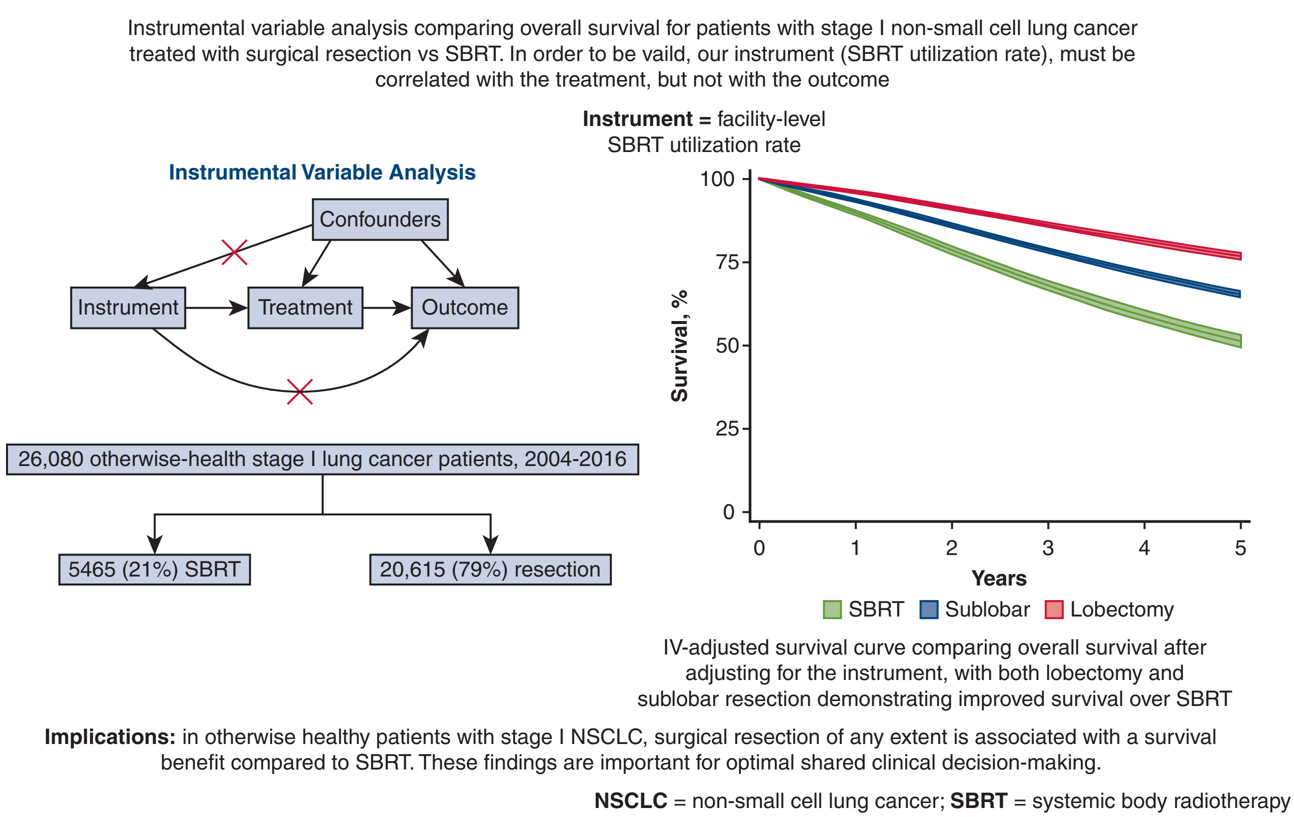
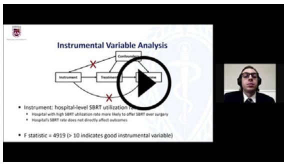


FIGURE 3. Depiction of overall findings of our work. We performed an instrumental variable analysis comparing overall survival for patients with stage I non–small cell lung cancer treated with surgical resection versus stereotactic body radiation therapy (*SBRT*). To be valid, our instrument, facility-level SBRT utilization rate, must be correlated with the treatment of interest, but not with the outcome. In our instrumental–variable (IV)-adjusted survival analysis, both lobectomy and sublobar resection were associated with improved survival relative to SBRT. These findings have important implications regarding optimal shared decision making. *NSCLC*, Non-small ling cancer.

benefit compared with SBRT. This is true for both lobar and sublobar resections. These findings are important for optimal shared decision making when considering treatment options.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to:https://aats.blob.core.windows.net/media/Publications/AATS%202021%20Littau%20and%20Pass.mp4.



Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: stereotactic body radiation therapy, stage I lung cancer, instrumental variable

Discussion

Presenter: Dr Michael John Littau

Dr Harvey I. Pass (*New York City, NY*). Esteemed moderators and American Association for Thoracic Surgery members, I want to congratulate the Loyola team, led by Mr Littau and Dr Abdelsattar for their novel statistical interpretation of the National Cancer Center Database (NCDB) with regard to the efficacy of stereotactic body radiation therapy (SBRT) compared with surgery for lesions smaller than 3 cm. Besides highlighting terrific mentorship and guiding a young medical student to collect and present these data, they offer both new and old insights into patient selection and counseling. There are some important take-home messages that may in fact alter how the NCDB will be interpreted in the future.

Using instrumental variable analysis in addition to the usual propensity matching analysis, the authors were able to show that their final modeling addressed both measured and unmeasured confounders that may be associated with an individual hospitals utilization rate of SBRT. But in reality, how do we know whether instrumental variable analysis is more useful because this is a novel method of data interpretation? Frankly, the only way I know to test how robust the statistical method is would be to see if the survivals of the surgery group, namely clinical T1a through T1c, are similar to the gold-standard survivals for the clinical stage cohort in the Eighth Edition of the International Association for the Study of Lung Cancer (IASLC) staging system. Indeed, the 5-year survival recorded for surgery in this NCDB cohort was 75%, compared with that established by the IASLC of 83%. Moreover, the surgical cohort analyzed by the usual propensity-score matching time-honored analysis had a 5-year survival of only 65%. Hence, at least for the surgical group, I think there's equipoise of how robust the data are.

In the comparison of the propensity matching between SBRT and surgery, the facility type and selected geographical locations of the facilities were significant factors in the Cox modeling for survival. As expected, when the utilization rate of SBRT was accounted for, facility variables were lost in the instrumental variable analysis once again revealing the superiority of both lobectomy and sub lobar receptions to SBRT for this cohort stage.

Nevertheless, there are the usual problems with granularity of the NCDB, mentioned by Mike, which the database will never be able to answer. My first issue is with the granularity of the staging process that's used in the NCDB. The NCDB presents us with the clinical stage, but we have no idea whether all the patients underwent positron-emission tomography-computed tomography, endobronchial ultrasound, or other invasive methods for staging. Moreover, in the same NCDB database, the role of lymph node sampling and survival in stage-I lung cancer has been demonstrated with various lymph node number cutoffs. At least 2 articles talk about whether it's 4 lymph nodes or 10 lymph nodes. So, unfortunately, using a clinical database we will never know whether the absence of lymph node sampling influences these results or whether or not just understaging of the SBRT group is responsible. My first question then is, Do you think that all patients who are to have SBRT should have preoperative invasive staging of the mediastinum because this could potentially alter their ultimate choice of therapy?

Dr. Michael John Littau (*Chicago, Ill*). Thank you, Dr Pass for the kind words and for facilitating this discussion. And thank you again to the American Association for Thoracic Surgery for the opportunity to present our work. It has been both my privilege and my pleasure to enter this debate with Dr Abdelsattar, and the rest of our team at Loyola.

Among the advantages to surgical resection over SBRT is the more exact tissue diagnosis and staging. Patients managed with SBRT alone do run the risk of being understaged and undertreated, with studies estimate that up to 35% of patients undergoing SBRT are understaged. For this reason, I do think it is important for patients choosing to undergo SBRT to undergo a potentially more invasive staging procedure. Unfortunately, like you mentioned, our database does not contain exact data on how these tumors were staged.

Dr Pass. Other key issues are to compare cohorts, including grading of the tumor: not just well, moderate, or poorly differentiated, but now we have the adenocarcinoma IASLC Histologic Grading System with grades 1 through 3. Is there balance between these issues? In fact, grading is reported in the NCDB database, but not alluded to in the presentation. Granted, you may only have at best core biopsies on some patients but did any of the SBRT patients have information on grading? Certainly, the surgical patients eventually would have these data, but it would be enlightening to see if there was any imbalance due to grading issues.

Dr Littau. We would have liked to consider grading in our study. However, as you mentioned, there were insufficient data in our SBRT cohort to effectively control for and or analyze these data. Fifty-nine percent of the SBRT group and missing data for grades. In contrast, only 6% of our surgery cohort did not have data on the grade of their disease.

For the patients we do have data available for, 18% of the SBRT cohort had fully differentiated histology compared with 21% of the surgery group, with more than one-half of the SBRT cohort having missing observations. We elected not to include this variable in our study.

Dr Pass. My final question is directed to what you tell patients. In counseling patients, do you think that your data are sufficient to tell patients who are fit for operation but who prefer nonsurgical therapy that their lung cancer survival is compromised with a nonsurgical decision? What do we do? Do we need to wait for the Veterans Affairs Lung Cancer Surgery or Stereotactic Radiotherapy trial to be analyzed before definitively counseling outpatients?

Dr Littau. This is of course the crux of the issue: How to counsel patients regarding their treatment options. Based on what is currently available in the literature, we believe that our study provides the most rigorous statistical methods, the largest population, and the most robust conclusions outside of a clinical trial. In our instrumental variable analysis, we demonstrated a significant survival benefit of both lobar and sublobar sections over SBRT.

With our results, bearing in mind the limitations of pathologic staging, we believe that patients should be counseled that surgery remains the gold standard of care for this disease. We look forward to data from the Veterans Affairs Lung Cancer Surgery or Stereotactic Radiotherapy trial. We're still 7 years away, especially regarding data on quality-of-life metrics. However, based on our data in previous studies we believe that surgery offers the best chance for a cure while SBRT is more likely to offer control rather than cure.

TABLE E1. Covariate balance across low-, mid-, and high-stereotactic body radiation therapy (SBRT) hospital utilization rates*

Variable	Low-SBRT utilization quintile SBRT rate = 1.9%		Mid-SBRT utilization quintile SBRT rate = 17.8%		High-SBRT utilization quintile SBRT Rate = 48.7%	
	Resection (%)	SBRT (%)	Resection (%)	SBRT (%)	Resection (%)	SBRT (%)
Age (%)						
<50 y	330 (6.5)	0 (0)	284 (6.5)	6 (0.6)	194 (7.3)	19 (0.8)
50-70 y	2802 (55)	23 (22.5)	2412 (55.6)	277 (29.6)	1454 (54.5)	789 (31.2)
>70 y	1963 (38.5)	79 (77.5)	1642 (37.9)	654 (69.8)	1018 (38.2)	1718 (68.0)
Sex (%)						
Female	2003 (39.3)	38 (37.3)	1716 (39.6)	400 (42.7)	1022 (38.3)	1076 (42.6)
Male	3092 (60.7)	64 (62.7)	2622 (60.4)	537 (57.3)	1644 (61.7)	1450 (57.4)
Race (%)						
White	4362 (85.6)	92 (90.2)	3818 (88.0)	822 (87.7)	2333 (87.5)	2270 (89.9)
Black	387 (7.6)	8 (7.8)	346 (8.0)	88 (9.4)	237 (8.9)	196 (7.8)
Other	319 (6.3)	1 (1.0)	137 (3.2)	20 (2.1)	81 (3.0)	39 (1.5)
Unknown	27 (0.5)	1 (1.0)	37 (0.9)	7 (0.7)	15 (0.6)	21 (0.8)
Surgery type (%)						
SBRT	0 (0)	102 (100)	0 (0)	937	0 (0)	2526 (100)
Wedge/segmentectomy	1360 (26.7)	0 (0)	887	0 (0)	532 (20.0)	0 (0)
Lobectomy	3735 (73.3)	0 (0)	3451	0 (0)	2134 (80.0)	0 (0)
Tumor size (%)						
<1 cm	387 (7.6)	3 (2.9)	258 (5.9)	28 (3.0)	140 (5.3)	78 (3.1)
1-2 cm	3158 (62)	60 (58.8)	2678 (61.7)	505 (53.9)	1626 (61.0)	1398 (55.3)
2-3 cm	1550 (30.4)	39 (38.2)	1402 (32.3)	404 (43.1)	900 (33.8)	1050 (41.6)
Insurance status (%)						
Private insurance	1803 (35.4)	13 (12.7)	1475 (34.0)	127 (13.6)	819 (30.7)	315 (12.5)
Government insurance	3090 (60.6)	87 (85.3)	2710 (62.5)	789 (84.2)	1745 (65.5)	2080 (82.3)
Uninsured	111 (2.2)	0 (0)	89 (2.1)	7 (0.7)	45 (1.7)	18 (0.7)
Unknown	91 (1.8)	2 (2.0)	64 (1.5)	14 (1.5)	57 (2.1)	113 (4.5)
Histology (%)						
Adenocarcinoma	3840 (75.4)	56 (54.9)	3172 (73.1)	450 (48)	1909 (71.6)	1221 (48.3)
Squamous cell carcinoma	853 (16.7)	29 (28.4)	840 (19.4)	298 (31.8)	544 (20.4)	779 (30.8)
Other	402 (7.9)	17 (16.7)	326 (735)	189 (20.2)	213 (8.0)	526 (20.8)
Diagnosis y (%)						
2004-2008	1187 (23.3)	26 (25.5)	896 (20.7)	181 (19.3)	544 (20.4)	431 (17.1)
2009-2012	1953 (38.3)	33 (32.4)	1811 (41.7)	334 (35.6)	1046 (39.2)	888 (35.2)
2012-2016	1955 (38.4)	43 (42.2)	1631 (37.6)	422 (45)	1076 (40.4)	1207 (47.8)
No high school diploma (%)						
≥17.6%	885 (17.4)	18 (17.6)	829 (19.1)	180 (19.2)	481 (18.7)	494 (19.6)
10.9%-17.5%	1137 (22.3)	25 (24.5)	1156 (26.6)	283 (30.2)	801 (30.0)	780 (30.9)
6.3%-10.8%	1489 (29.2)	34 (33.3)	1256 (29.0)	252 (26.9)	736 (27.6)	722 (28.6)
<6.3%	1545 (30.3)	23 (22.5)	1065 (24.6)	213 (22.7)	615 (23.1)	497 (19.7)
Unknown	39 (0.8)	2 (2.0)	32 (0.7)	9 (1.0)	33 (1.2)	33 (1.3)
Income quartile (%)						
<25%	657 (12.9)	12 (11.8)	832 (19.2)	205 (21.9)	499 (18.7)	542 (21.5)
25%-50%	848 (16.6)	23 (22.5)	1048 (24.2)	225 (24.0)	668 (25.1)	684 (27.1)
50%-75%	1009 (19.8)	20 (19.6)	990 (22.8)	217 (23.2)	750 (28.1)	665 (26.3)
>75%	2530 (49.7)	45 (44.1)	1430 (33.0)	281 (30.0)	713 (26.7)	593 (23.5)
Unknown	51 (1.0)	2 (2.0)	38 (0.9)	9 (1.0)	36 (1.4)	42 (1.7)

*Second and fourth quintiles not shown for simplicity.