

# Treatment of Stage I Lung Cancer Detected by Computed Tomography Screening



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## ABSTRACT

**Introduction:** Reducing lung cancer deaths through early detection by computed tomography (CT) screening requires delivery of effective treatment. We performed this retrospective study to determine the types of treatment used for screen-detected stage I lung cancer at our academic center and to compare the demographic and clinical characteristics of patients by type of treatment.

**Methods:** All persons screened in the lung cancer screening program at our institution through June 16, 2021, were included. Those with screening CT findings needing follow-up were managed through a thoracic surgery clinic. Demographic and clinical characteristics of patients diagnosed with having stage I lung cancer through June 16, 2021, were compared by type of treatment, with follow-up through December 31, 2021.

**Results:** Stage I NSCLC was diagnosed in 54 of 2203 persons screened (2.5%), on the basis of biopsy in 37 and on imaging findings in 17 patients in whom a tissue diagnosis could not be obtained. Treatment was by lobectomy in 18, sublobar resection in 14, and stereotactic body radiation therapy (SBRT) in 22. Patients treated with SBRT had lower forced expiratory volume in 1 second ( $p < 0.001$ ) and diffusing capacity of the lung for carbon monoxide ( $p < 0.001$ ) and more comorbidities ( $p = 0.003$ ) than those treated with surgery. New or recurrent cancer developed in nine patients (three lobectomy, three sublobar resection, three SBRT).

**Conclusions:** Many patients with screen-detected stage I lung cancer are medically unfit for lobectomy, and a variety of treatments are being used. Assessment of treatment-based outcomes will be critical for ensuring an optimal balance of the risks and benefits of CT screening in a medically diverse population.

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**Keywords:** Lung cancer; Screening; CT; Treatment

## Introduction

Reducing lung cancer mortality through computed tomography (CT) screening relies on detecting the disease at an early stage and delivering effective therapy. Complete surgical resection by lobectomy is considered the treatment of choice. Current recommendations discourage CT lung cancer screening (LCS) for those unable or unwilling to undergo curative surgery.<sup>1</sup> Nevertheless, screening typically is performed before operability is known.

If the treatment of patients with screen-detected early stage lung cancer differs in clinical practice

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compared with clinical trials that revealed the effectiveness of screening, patient outcomes also may differ. We performed this study to determine the treatments used for patients with screen-detected stage I lung cancer in our academic center and to compare demographic and clinical characteristics of those treated with and without surgery.

## Materials and Methods

This retrospective study was approved by our Institutional Review Board with waiver of consent. The study cohort consisted of all persons who had annual low-dose CT examinations in our LCS program from September 18, 2016, to June 15, 2021. Eligibility for screening was determined by the 2014 recommendation statement of the U.S. Preventive Services Task Force<sup>1</sup> and included age 55 to 80 years, minimum smoking history of 30 pack-years, and abstinence from smoking for no more than 15 years.

CT scan interpretation and management recommendations followed the American College of Radiology LungRADS system.<sup>2</sup> Those with findings warranting additional evaluation (LungRADS categories 3 and 4) were referred to one of five thoracic surgeons, who made management decisions regarding imaging surveillance, biopsy, and resection. Patients considered inoperable were referred to one of 10 radiation oncologists who made subsequent decisions regarding stereotactic body radiation therapy (SBRT).

Electronic medical records of those diagnosed with having stage I lung cancer by June 15, 2021, were reviewed through December 31, 2021. Patient characteristics were compared across treatment groups using two-tailed paired *t* tests for continuous variables and chi-square tests for categorical variables (Microsoft Excel) with *p* values less than 0.05 considered significant. Cancer outcomes including local recurrence, metastasis, new primary, and death were recorded, without statistical comparison between treatment methods owing to small number of events and limited follow-up duration.

## Results

At least one screen was performed in 2203 persons; of 1418 eligible (no lung cancer or death) for at least one annual repeat screen within 1.5 years of their first annual screen, 936 (66%) had at least one annual repeat screen. Lung cancer was diagnosed in 81 of 2203 (3.7%) and was determined to be stage I in 54 patients (2.5% of patients screened, 67% of all lung cancers). The cancer was identified on the initial screen in 41 of 54 stage I cancers (76%), and nine of these patients had progressed in comparison to a previous non-LCS CT scan.

In the other 13 of 54 patients (24%), the cancer first appeared on an annual repeat screen. Diagnosis and staging were on the basis of tissue sampling and imaging in 37 patients (all non-small cell) and on imaging alone (serial CT and positron emission tomography-CT) in 17 patients in whom a tissue diagnosis could not be obtained (Fig. 1A–D).

Of the 54 patients diagnosed with having stage I lung cancer, 18 (33%) were treated with lobectomy, 14 (26%) with sublobar resection (five by segmentectomy, nine by wedge resection), and 22 (41%) with SBRT. Five of the 37 patients with a histologic diagnosis (14%) and all 17 without histologic confirmation were treated with SBRT. None received chemotherapy.

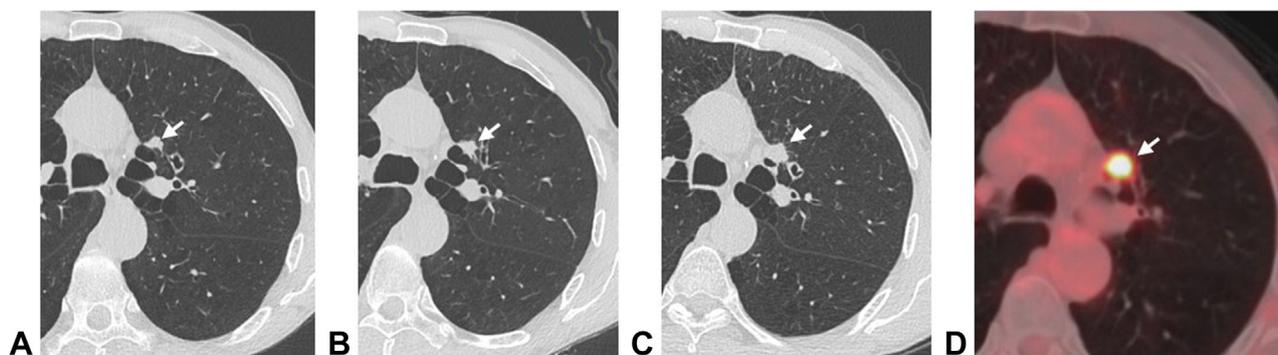
Table 1 illustrates that compared with those treated with any surgery, patients treated with SBRT had lower lung function as measured by forced expiratory volume in 1 second and diffusing capacity of the lung for carbon monoxide (both  $p < 0.001$ ) and more comorbidities ( $p = 0.003$ ). Although patients treated with lobectomy and sublobar resection had similar clinical characteristics, those treated with sublobar resection had smaller lung nodules ( $p = 0.003$ ). More non-white patients were treated with SBRT (not statistically significant) but also had lower lung function (mean  $\pm$  SD forced expiratory volume in 1 second %predicted  $71 \pm 14$  versus  $83 \pm 16$ ,  $p = 0.02$ ; diffusing capacity of the lung for carbon monoxide %predicted  $44 \pm 15$  versus  $61 \pm 19$ ,  $p < 0.01$ ), and more had a history of stroke (7 of 54 [13%] versus 2 of 54 [4%],  $p < 0.01$ ).

Mean follow-up time was 2.0 plus or minus 1.1 years. Three patients developed local recurrence, two developed liver metastases, and four developed new primary lung cancers; one patient died of lung cancer and four died from other causes (Supplementary Table 1).

## Discussion

In this cohort, 2.5% (54 of 2203) of screened patients were diagnosed with having stage I lung cancer, one-third of whom were treated with lobectomy and a larger proportion (41%) of whom were treated non-surgically using SBRT. Those not treated with surgery had worse lung function and more comorbidities, corroborating the clinical decisions. Neither biopsy nor surgery could be performed in 17 (31%), with diagnosis, staging, and treatment by SBRT on the basis of imaging findings alone.

These observations contrast with those of the National Lung Screening Trial (NLST), in which 1.2% had screen-detected stage I lung cancer, 78% of whom were treated with lobectomy and 91% with any surgery (estimated 10-y survival of 74%),<sup>3</sup> and with the International Early Lung Cancer Action Project (I-ELCAP), in which the corresponding numbers were 1.3%, 81%, and



**Figure 1.** A 66-year-old male current smoker with 30 pack-year smoking history. (A) Lung cancer screening CT scan result reveals 7-mm average diameter nodule (arrow) in the left upper lobe. (B) Follow-up scan result 4 months after considered stable. (C) Follow-up scan result 10 months after (A) reveals nodule enlargement to 1.4 cm. (D) PET-CT result reveals FDG uptake in the nodule with SUV 13.4. Biopsy was not pursued owing to the central location of the nodule. Lung function was considered inadequate for surgical resection, and SBRT was performed. CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; SBRT, stereotactic body radiation therapy; SUV, standardized uptake value.

95% (estimated 10-y survival of 88%), respectively.<sup>4</sup> In addition, the proportion of participants in the NLST with comorbidities was much lower than that in our cohort.<sup>5</sup> Our findings suggest that the clinical characteristics, cancer rate, and operability of those screened in clinical practice may not reflect those of the participants in LCS trials. Specifically, patients in clinical practice may be at higher risk for lung cancer, and more may have comorbidities that limit operability. In our cohort, the rate of adherence to at least one annual repeat screening (66%) was lower than that in the NLST (95%) and I-ELCAP (87%), so actual cancer rates may even have been underestimated. It should also be noted that SBRT was not in use during the trials.

Lobectomy has long been considered the treatment of choice for stage I lung cancer owing to lower locoregional recurrence and death rates than with limited resection (segmentectomy or wedge).<sup>6</sup> In practice, however, surgeons frequently perform sublobar resection, particularly in patients at higher surgical risk. Retrospective observational studies reveal that outcomes may depend on patient selection. An analysis of the Surveillance, Epidemiology, and End Results database found no difference in lung cancer-specific survival by extent of resection with tumors 1.0 cm or smaller; no difference between lobectomy and segmentectomy for tumors 1.1 to 2.0 cm, but better survival than with wedge resection; and superior survival with lobectomy compared with segmentectomy or wedge resection for tumors 2.1 to 3.0 cm.<sup>7</sup> An analysis of the National Cancer Database found overall survival differences related to both size and biopsy, with lobectomy superior to segmentectomy for adenocarcinoma larger than 10 mm and for squamous cell carcinoma larger than 15 mm.<sup>8</sup> In a different cohort from the same database, 5-year overall survival was equivalent for lobectomy

and sublobar resection, but the number of lymph nodes sampled was lower and recurrence rates were 39% higher in the sublobar group.<sup>9</sup> Retrospective analyses of data from I-ELCAP<sup>10</sup> and NLST<sup>11</sup> both found equivalent survival of screen-detected stage I lung cancer with lobectomy or sublobectomy. These findings may support a role for sublobar resection in selected patients, as was done in a subgroup of our patients who had smaller nodules.

SBRT is now the treatment of choice for patients with stage I lung cancer who are medically inoperable.<sup>12</sup> In several cooperative trials, SBRT achieved local control in 83% to 93% of inoperable patients with early stage lung cancer at 5 years and locoregional or regional control in 65% to 84%, with 5-year overall survival of 40% to 56%.<sup>12</sup> This lower overall survival compared with historical surgical cohorts may be related to the comorbidities that result in inoperability. Treatment-related morbidity and mortality associated with central or paramediastinal tumors or pulmonary fibrosis also may affect the effectiveness of SBRT. Lack of histologic diagnosis and staging before SBRT, as in a substantial proportion of our cohort, has potential for understaging and overdiagnosis.

Uncertainty regarding the relative efficacy of different treatments in the population currently being screened for lung cancer may limit the overall benefit of LCS in the real-world clinical setting. The differences in patient characteristics and treatment compared with clinical trials observed here emphasize the need to study these components of LCS and long-term outcomes on a large scale. Favorable outcomes of the different treatments, even if not equivalent, would support current screening practices. Poor outcomes in patient or treatment subgroups may warrant reconsideration of how screening eligibility is determined or patients are

Table 1. Characteristics and Treatment of Patients With Screen-Detected Stage I Lung Cancer

Characteristic	Lobectomy (n = 18)	Sublobar Resection (n = 14)	SBRT (n = 22)	Any surgery (Lobectomy + Sublobar Resection) (n = 32)	p Value (Any Surgery vs. SBRT) (n = 54)	p Value (Lobectomy vs. Sublobar Resection) (n = 32)
Age, y	64.6 (SD 5.5)	65.8 (7.2)	65.8 (SD 5)	65.1 (SD 6.3)	0.31	0.58
Women, n (%)	9 (50)	11 (78)	10 (45)	20 (63)	0.22	0.10
Non-white patients, <sup>a</sup> n (%)	6 (33)	4 (29)	16 (73)	9 (28)	0.001	0.96
Pack-years smoked, n (%)	44 (16)	39 (15)	48 (16)	42 (15)	0.14	0.37
Current smokers, n (%)	15 (83)	11 (79)	17 (77)	26 (81)	0.72	0.73
BMI, kg/m <sup>2b</sup>	25 (SD 8)	29 (SD 6)	27 (SD 7)	27 (SD 7)	0.82	0.17
FEV <sub>1</sub> , %predicted	87 (SD 17)	84 (SD 13)	65 (SD 18) <sup>c</sup>	86 (SD 15)	<0.001	0.58
D <sub>L</sub> CO, %predicted	64 (SD 18)	58 (SD 19)	41 (SD 14) <sup>d</sup>	61 (SD 18)	<0.001	0.35
Total comorbidities	1.6 (SD 1.5)	1.4 (SD 1.1)	2.6 (SD 1.2)	1.5 (SD 1.3)	0.003	0.72
Comorbidity, n (%)						
COPD/emphysema	8 (44)	5 (36)	15 (68)	12 (40)	<0.05	0.61
Hypertension	11 (61)	7 (50)	18 (82)	16 (53)	0.05	0.52
Diabetes	4 (22)	5 (36)	9 (41)	8 (27)	0.33	0.40
CHF	1 (6)	0 (0)	2 (9)	1 (3)	0.35	0.37
CAD	3 (17)	2 (14)	6 (27)	4 (13)	0.30	0.85
Stroke	2 (11)	0 (0)	7 (33)	2 (7)	0.013	0.20
Nodule size, cm	2.1 (SD 1.0) <sup>e</sup>	1.1 (SD 0.3)	1.8 (SD 0.8)	2.2 (SD 1.0)	0.37	0.003

<sup>a</sup>All black except for one Native American who had lobectomy.

<sup>b</sup>Preop BMI not available for one patient who had sublobar surgery.

<sup>c</sup>PreTx FEV<sub>1</sub> not available for two patients who had SBRT.

<sup>d</sup>D<sub>L</sub>CO not available for two patients who had SBRT.

<sup>e</sup>Nodule size excluded in four patients treated with lobectomy (two with endobronchial nodules, one with mixed consolidation and ground-glass opacity, and one with a mixed ground-glass and solid nodule).

BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; D<sub>L</sub>CO, diffusing capacity of the lung for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; Preop, preoperative; PreTx, pretreatment; SBRT, stereotactic body radiation therapy.

treated. Although our cohort size is insufficient and follow-up duration is too short to compare treatment outcomes, the observed treatment failures illustrate the unfortunate reality that neither surgery nor SBRT guarantees long-term tumor-free survival.

This study is limited by a small cohort size from a single LCS program. Nevertheless, other screening centers also have found that patient characteristics differ between the NLST and real-world programs<sup>13</sup> and an increasing proportion of all patients with stage I lung cancer are being treated with SBRT.<sup>14,15</sup> This suggests that our experience may be occurring on a much larger scale. With widespread implementation of LCS, evaluating outcomes for diverse patients who undergo different treatments will be critical for optimizing the balance of benefits and risks.

## CRedit Authorship Contribution Statement

**David S. Gierada:** Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Writing—original draft, Writing—review and editing, Project administration.

**Yun Zhu Bai:** Methodology, Investigation, Writing—review.

**Matthew B. Spraker:** Conceptualization, Writing—review and editing.

**Anne Stilinovic:** Investigation, Writing—review.

**Ruben G. Nava:** Conceptualization, Methodology, Writing—review and editing, Project administration.

## Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at <http://www.jtocrr.org> and at <https://doi.org/10.1016/j.jtocrr.2022.100399>.

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