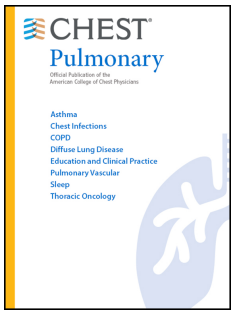

Protocol for the Veterans Affairs Cooperative Studies Program Study #2005: A Phase III Randomized Trial of Lung Cancer Surgery or Stereotactic Radiotherapy for Operable Early-Stage Non-Small Cell Lung Cancer (VALOR)

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PII: S2949-7892(23)00024-7

DOI: https://doi.org/10.1016/j.chpulm.2023.100024

Reference: CHPULM 100024

To appear in: *CHEST Pulmonary*

Received Date: 13 April 2023

Revised Date: 14 August 2023

Accepted Date: 30 August 2023

Please cite this article as: Moghanaki D, Karas T, Timmerman RD, Cameron RB, Ritter TA, Shi H, Leiner MK, Feng H, Skinner VL, Robin L, Odle C, Sindowski T, Snodgrass AJ, Huang GD, Reda DJ, Harpole DH, On behalf of the VALOR study team, Protocol for the Veterans Affairs Cooperative Studies Program Study #2005: A Phase III Randomized Trial of Lung Cancer Surgery or Stereotactic Radiotherapy for Operable Early-Stage Non-Small Cell Lung Cancer (VALOR), *CHEST Pulmonary* (2023), doi: https://doi.org/10.1016/j.chpulm.2023.100024.

Abstract Word Count: 281
Text Word Count: 3,203

Title: Protocol for the Veterans Affairs Cooperative Studies Program Study #2005: A Phase III Randomized Trial of Lung Cancer Surgery or Stereotactic Radiotherapy for Operable Early-Stage Non-Small Cell Lung Cancer (VALOR)

Running Title: VALOR Study Protocol

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[a] Drs. Niewoehner and Provenzale were instrumental in helping develop the study protocol that is summarized in this manuscript. As listed in the appendix, they were official members of our Study Planning Committee between 2013-2017 and later transitioned to serve as members of our Executive Committee until their passing in 2020 and 2021, respectively. While Drs. Niewoehner and Provenzale never saw any drafts of the manuscript, the substance of the manuscript includes their contributions through dozens of telephone conferences, emails, and face-to-face meetings over a 7–8-year period.

Abstract Word Count: 281
Text Word Count: 3,203

Acknowledgements

Sponsor: The Department of Veterans Affairs Cooperative Studies Program (VA CSP) funded this study as CSP #2005, Veterans Affairs Lung Cancer Surgery Or Stereotactic Radiotherapy (VALOR).

Conflict of interest: DM reports speaking honoraria related to educational programs for Varian Medical Systems, ViewRay Technologies, and Accuray, Inc. and consulting services for ViewRay Technologies. RDT reports grants or contracts from Varian Medical Systems, Elekta Oncology, and Accuray, Inc. RBC reports payment for expert witness testimony for medical legal actions, patents for a chest tube insertion device and bubble detector, and common stock in Medtronic. TAR reports salary support in the form of a salary offset from the VA Cooperative Studies Program, Hines IL as an employee of the Veterans Health Administration. The support did not include any additional compensation above his standard federal salary. All other authors have no conflicts to disclose.

Disclaimer: The contents of this report do not represent the views of the United States Department of Veterans Affairs or the United States Government.

Guarantor: DM takes responsibility for the content of this manuscript.

Author contributions: All authors substantially contributed to the conception and design of the study, participated in drafting the article and revising it critically for intellectual content, and reviewed and approved the final submitted version.

Other contributions: The VALOR study team thanks Professor Jenny Donovan for her collaboration and contributions to the development of recruitment methods utilized in this study through the QuinteT Recruitment Intervention-Two.

Key Words List

Early-stage; Clinical trial; Lobectomy; Non-small cell lung cancer; Phase III; Randomized; Segmentectomy; Stereotactic body radiation therapy; Thoracic surgery

Abbreviations List

ACOSOG – American College of Surgeons Oncology Group
AJCC – American Joint Commission on Cancer
CSP – Cooperative Studies Program
DMC – Data Monitoring Committee
EORTC QLQ-C30 – The European Organization for Research and Treatment of Cancer core quality of life questionnaire
EQ-5D-5L – EuroQol 5 Dimension 5 Level quality of life questionnaire
FDG-PET – fluorodeoxyglucose-positron emission tomography
FDR – false discovery rate
FEV – forced expiratory volume
Gy – Grays, units used to measure the total amount of radiation a patient is exposed to
LC13 – lung cancer-specific 13-item questionnaire module
NRG – National Surgical Adjuvant Breast and Bowel Project (NSABP), the Radiation Therapy Oncology Group (RTOG), and the Gynecologic Oncology Group (GOG)
NSCLC – non-small cell lung cancer
OS – overall survival
QOL – quality of life
QRI-Two – QuinteT Recruitment Intervention-Two
QuinteT – Qualitative research integrated in Trials
RECIST – response evaluation criteria in solid tumors
RTOG – Radiation Therapy Oncology Group
SBRT – stereotactic body radiation therapy
STARS – Stereotactic ablative radiotherapy for operable stage I non-small-cell lung cancer trial
VA – Veterans Affairs
VALOR – Veterans Affairs Lung Cancer Surgery Or Stereotactic Radiotherapy

Abstract

Background: Standard of care treatment options for stage I non-small cell lung cancer (NSCLC) include surgery and stereotactic body radiation therapy (SBRT). Notwithstanding a lack of prospective evidence demonstrating superior long-term survival with either of these treatments, evidence-based guidelines currently only recommend surgery for operable patients and limit SBRT for inoperable patients.

Research Question: Does surgery or SBRT lead to superior survival rates for operable stage I NSCLC?

Study Design and Methods: A phase III randomized clinical trial was designed to compare the overall survival (OS) rates following surgery or SBRT for stage I NSCLC. Eligible participants must have biopsy confirmed NSCLC measuring ≤5 cm in maximum diameter located >1 cm from the trachea, proximal bronchial tree, esophagus, and spinal cord. Participants must be staged with fluorodeoxyglucose-positron emission tomography scans with mandatory biopsies of all radiographic areas concerning for regional or distant metastatic disease. The planned accrual is 670 patients to detect a 10% absolute benefit in 5-year OS with surgery or SBRT. Secondary outcome measures include patient reported quality of life, respiratory function, health state utilities, patterns of lung cancer relapse, and causes of mortality by independent adjudication.

Results: The study was activated in April 2017 with a planned ramp-up phase at six Veterans Affairs medical centers. Adapted recruitment interventions contributed to successfully overcoming historical barriers to randomizing eligible participants between surgery and SBRT, and the study was expanded to 16 sites in May 2019. As of July 5, 2023, 280 of 670 planned participants have been enrolled.

Interpretation: The final results are expected to clarify the role of SBRT in lieu of surgery for patients with operable stage I NSCLC and facilitate more informed discussions about these treatment options.

Clinical Trials Registration Number: NCT02984761

Introduction

Current evidence-based guidelines for stage I non-small cell lung cancer (NSCLC) recommend anatomic lung resection (lobectomy or segmentectomy) with stereotactic body radiation therapy (SBRT) being an alternative in patients who cannot tolerate surgery. Notwithstanding a lack of prospective evidence demonstrating superior long-term survival with either treatment, evidence-based guidelines currently only recommend surgery for operable patients while limiting SBRT for inoperable patients.

In the 1950's, investigators at the Hammersmith Hospital in London completed a randomized trial of surgery versus radiation therapy in 58 patients with early-stage NSCLC.[1] The results were published in 1963 and demonstrated superior 4-year OS in the surgery group (7-23% vs 2-7%). The study was conducted prior to development of the CT scanner, undoubtedly under-staging patients in both arms, and relied on obsolete supervoltage radiation therapy technologies delivering an insufficient dose (45 Gy). Nonetheless, the results from that trial provide the highest level of evidence supporting surgical resection as the only guideline-endorsed standard of care for operable early-stage NSCLC.

More contemporary prospective single-arm phase I and II clinical trial results suggest SBRT offers a treatment that can provide equivalent overall survival (OS) outcomes compared to surgery with a safer treatment profile.[2,3] Retrospective studies comparing surgery and SBRT with observational datasets are confounded by selection bias and considered unreliable in determining the potential advantage of either treatment for operable patients.[4,5,6] Five prospective randomized clinical trials comparing SBRT versus surgery were attempted between 2008-2015, and all were terminated after enrolling only a combined total of 91 out of 1,950 planned participants, underscoring the difficulty of conducting such a definitive trial.[7,8,9,10,11] A pooled analysis of limited data from two of these studies (n=58) demonstrated a 3-year OS rate of 95% after SBRT versus 79% in the surgery group; however, the data were deemed insufficient for extrapolation due to the small sample size.[12,13] A subsequent non-randomized comparison of prospectively confirmed operable patients treated with SBRT (n=80) demonstrated non-inferior OS as compared to a propensity matched cohort of patients (n=80) treated with video assisted thoracoscopic lobectomy and mediastinal lymph node dissection with appropriate adjuvant therapy in the 10% who were found to harbor pathologically involved regional lymph nodes; the 3-year OS was 91% in both cohorts and 5-year OS was 87% vs 84% favoring SBRT.[12]

Given the promising long-term survival rates demonstrated in prospective clinical trials of patients with stage I NSCLC treated with SBRT, a sufficiently powered randomized clinical trial may demonstrate superior OS with this non-operative treatment and challenge clinical guidelines that currently only recommend surgery for an operable population.

Study Design and Methods

The phase III randomized clinical trial, Veterans Affairs Lung Cancer Surgery Or Stereotactic Radiotherapy (VALOR), was designed to compare the OS of patients with operable early-stage NSCLC treated with SBRT or anatomic resection. The study is designed to enroll participants with a long life-expectancy to minimize confounding of the primary objective with competing risks from intercurrent deaths unrelated to lung cancer relapse or treatment.

This is a multi-center, unblinded, randomized clinical trial with parallel assignment to determine whether patients with clinical stage I NSCLC have higher OS following surgery or SBRT. Participants considered for the trial must be eligible for both treatment arms and are randomized with a 1:1 ratio. The schema of the study design is presented in Figure 1.

The study aims to randomize 670 study participants at ≥16 enrollment sites to receive either surgery or SBRT. All randomized participants will be followed through the end of study. The duration of the study is 15 years, which allows for 10 years of recruitment and 5 years of minimum follow-up. The primary outcome measure is time from randomization to the event of death from any cause to compare the OS rate between participants treated with surgery or SBRT. Secondary outcome measures are organized with a hierarchical model to compare the following: patient reported quality of life (QOL), respiratory function assessed by patient reported surveys, respiratory function assessed by pulmonary function testing, health state utilities, lung cancer-specific mortality, and patterns of relapse during post-treatment surveillance (see Figure 2).

Participant Eligibility

Participants are primarily recruited through primary care and pulmonology clinics to optimize equipoise, although recruitment from thoracic surgery and other clinics is allowed. To be eligible, participants must be at least 18 years of age, have a Karnofsky performance status ≥70, be willing to be treated with either surgery or SBRT, and be able to provide informed consent. All participants must have biopsy-proven clinical stage IA-IB NSCLC according to the American Joint Commission on Cancer (AJCC) 7th edition. The maximum tumor dimension must be ≤5 cm as measured by diagnostic computed tomography (CT) scans and located >1 cm from the trachea, proximal bronchial tree, esophagus, brachial plexus, and spinal cord. Required staging studies include a fluorodeoxyglucose-positron emission tomography (FDG-PET) scan within 60 days of randomization with mandatory pathological assessment of any radiographically visualized lymph nodes measuring >1 cm in size with a standard uptake value >2.5, and a biopsy of any other concerning lesions seen on pre-randomization images. Elective lymph node sampling via endobronchial ultrasound or mediastinoscopy is strongly encouraged before randomization, but not required. Participants must have a pre-operative forced expiratory volume $(FEV)_1$ >40% and diffusing capacity for carbon monoxide (DLCO) >40% of predicted value, be deemed eligible for an anatomic lung resection (lobectomy or segmentectomy) by a thoracic surgeon, be deemed eligible to receive SBRT by a radiation oncologist, and have their case reviewed at a multidisciplinary conference with confirmation of the clinical stage.

Participants are ineligible if they have had any prior history of lung cancer, thoracic surgery for lung or esophageal cancer (prior cardiac surgery acceptable), radiotherapy to the thorax, invasive malignancy within the past 5 years (whether newly diagnosed or recurrent, excluding low or intermediate-risk prostate cancer with a Gleason score of ≤ 7, non-melanoma skin cancers, and in-situ cancers), a diagnosis of stage IV cancer of any type, scleroderma, or positive pregnancy test.

Stratification and Randomization

Participants are centrally randomized 1:1 to either the surgery or SBRT arms utilizing a permuted block scheme with random block sizes after stratification by: (1) study site, (2) tumor size ≤3 cm vs 3-5 cm, and (3) tumor location (peripheral vs central). Centrally located tumors are defined based on guidelines published in 2015 by the International Association for the Study of Lung Cancer[14]; whenever the tumor is ≤2 cm from the spinal canal, proximal bronchial tree, brachial plexus, esophagus, heart (including pericardium), or great vessels it is a central tumor according to the protocol.

Treatment Interventions
Participants randomized to surgery will undergo an anatomic resection with lobectomy or anatomic segmentectomy at the discretion of the thoracic surgeon with intraoperative lymph node sampling of at least one hilar and two mediastinal stations. Following surgery, operative and pathological reports will be centrally reviewed to confirm the pulmonary artery and bronchus were separately divided to confirm an anatomic resection was performed; non-anatomic (wedge) lung resections are not permitted. Central quality reviews will also confirm that at least one hilar and two mediastinal stations were sampled.

Participants randomized to SBRT will be treated with 3-5 fractions (daily or every-other-day) with a prescription that achieves a biologically effective dose ≥100 Gy. Tumors classified as central must be treated with 10 Gy x 5 fractions, while peripheral lesions can be treated with any of the following prescriptions: 18 Gy x 3 fractions, 14 Gy x 4 fractions, or 11.5 Gy x 5 fractions. The primary tumor is treated with SBRT without a clinical tumor volume margin expansion to account for potential microscopic extension beyond radiographic detection. The planning tumor volume includes a mandatory 5 mm to 7 mm expansion of the primary tumor volume for daily setup uncertainties. There is no elective coverage of the hilar or mediastinal lymph nodes. SBRT treatment plans must not exceed protocol-defined threshold dose limits for critical normal structures defined as the spinal canal, esophagus, trachea, proximal bronchial tree, or brachial plexus. Additional technical parameters for the delivery of SBRT are defined in the study protocol which was developed in accordance with standards established by the NRG Oncology Group and are subject to modification during the study if scientific developments lead to changes in best practice. Central quality reviews following treatment delivery will confirm that the SBRT delivery requirements were met according to the protocol.

Post-Treatment Assessments
Following surgical resection or SBRT, all participants are assessed during scheduled in-person, video, or telephone appointments three times in the first year (3, 6, and 12 months), and every 6 months thereafter for a minimum of 5 years of follow-up. In the event that higher stage disease is discovered at time of surgery, or during post-treatment surveillance after either treatment, additional lung cancer therapies are recommended in accordance with contemporary evidence-based guidelines and multi-disciplinary review. There are no required visits or adverse event monitoring after 5 years; however, vital status and cause of death will continue to be recorded and centrally reviewed until the end of the study. Participants who miss a scheduled research appointment are contacted for rescheduling, and the vital status of any participant who can no longer be contacted will be queried through Veterans Affairs (VA) and other administrative databases at the end of the study to minimize censoring of the primary outcome measure of OS.

Changes in QOL and health state utilities will be compared at 3, 6, and 12 months and annually thereafter with the following patient reported surveys: the European Organization for Research and Treatment of Cancer core QOL questionnaire (EORTC QLQ-C30), EORTC lung cancer-specific 13-item questionnaire module (LC13), and the EuroQol 5 Dimension 5 Level (EQ-5D-5L) QOL questionnaire.[15,16] Changes in breathing will be compared at 3 and 12 months, and annually thereafter using the St. George's Respiratory Questionnaire and pulmonary function tests.[17]

Causes of mortality for each participant who dies during the study are assessed by an independent mortality adjudication committee of three physicians, excluding the study chairs, and adjudicated by a majority. Whenever participants die at home, or outside the VA, the deceased participant's local study team will gather all potential sources of information to help

the independent adjudication committee make a cause of mortality determination. Mortality cause adjudication is un-blinded, given the challenges of concealing the history of prior surgery or SBRT.

Comparisons of radiographic patterns of failure were given the lowest priority in the hierarchical model of secondary outcome measures given the known difficulties in discerning tumor recurrence within an area of evolving fibrosis following SBRT.[18] Patterns of relapse (local, regional, and distant) will be assessed with scheduled post-treatment CT surveillance scans of the chest and abdomen performed three times in the first year (3, 6 and 12 months), and every 6 months thereafter. Comparisons rely on a scoring system adapted from the American College of Surgeons Oncology Group (ACOSOG) Z4099/Radiation Therapy Oncology Group (RTOG) 1021 phase III study that specifies instructions for the surgery and SBRT arms (see Table 1). For internal quality purposes only, tumor response to SBRT will be separately coded using response evaluation criteria in solid tumors (RECIST) v1.1 criteria, with the addition of a "cannot be determined" category whenever measurements of the primary tumor site are obscured by post-radiation reaction.

Statistical Plan

To evaluate the efficacy of SBRT compared to surgery, the primary outcome will be OS, defined as the time from randomization to death from any cause. A sample size of 670 participants is required to obtain at least 85% power to detect a 10% absolute benefit in 5-year OS rate with surgery of SBRT at the 0.05 significance level, assuming a 9% drop out rate after randomization. The surgery group is hypothesized to have a 5-year OS rate of 65% based on the following data: (1) results from population-based surgical series reporting a range of 5-year OS of 58-77%,[19,20] (2) results from the ACOSOG Z0030 study that randomized over 1,000 operable patients in the US with stage I NSCLC between lymph node sampling and dissection reporting a 5-year OS rate of 69%,[21] and (3) protocol defined estimates in two similar phase III trials that predicted a 3-year OS of 80% (ACOSOG-Z4099/RTOG-1021) and 82% (Stereotactic ablative radiotherapy for operable stage I non-small-cell lung cancer trial (STARS)) in the surgery arms.[7,8]

The primary analysis of OS among randomized participants will utilize Kaplan-Meier estimations of survival patterns and the log-rank test based on the intent-to-treat principle. Secondary analyses of OS will use regression models to compare treatment groups by tumor stage (IA or IB), tumor location (peripheral or central), and tumor type (adenocarcinoma or squamous cell carcinoma). Interaction terms between treatment groups and stratification variables will investigate whether these pre-treatment variables are predictive for improved survival by treatment group. A per-protocol sensitivity analysis will be performed to compare OS for participants who adhered to their assigned treatment and did not have any major protocol deviations. Additional analyses will evaluate participants who later enroll in a separate lung cancer clinical trial for surgical upstaging or clinical progression using the methods described for the primary analysis assigning additional treatment interventions as a covariate in the regression models.

Regarding the twelve secondary outcome measures listed in Figure 2, the overall type I error rate will be controlled using a hierarchical gatekeeping structure with two families. Comparisons of secondary outcome measures in the second family will only occur if at least one outcome is significant in the first family. The first family includes patient reported health-related QOL measured with the QLQ-C30/LC-13 survey instruments that will be compared at two time points: 3 months and 5 years. The second family consists of a total of 9 end points that include subjective and objective measures of respiratory function by measuring the total score on the

St. George's Respiratory Questionnaire and predicted FEV1 values, each compared at 3 months and 5 years. Additional measures in this second family include comparisons of health state utilities analyzed with quality-adjusted life years using the EQ-5D, Kaplan-Meier comparisons of lung cancer mortality, and Kaplan-Meier comparisons of patterns of tumor relapse that include local, regional, and distant disease progression. Each hypothesis in the first family will be tested against a type I error rate of 0.05/2=0.025 to maintain an overall error rate of 0.05 in this family. [22] The false discovery rate (FDR) is set at 0.05 (i.e., q=0.05) to determine significant hypotheses in the second family using a procedure by Benjamini and Hochberg.[17] The error rate of this FDR approach is equivalent to the familywise error rate when all null hypotheses are true, and smaller otherwise.

Study Management and Monitoring

The study is approved by the VA Central Institutional Review Board and managed by the VA Cooperative Studies Program (CSP) Coordinating Center at the Edward Hines Jr. VA Hospital. The study receives subject matter guidance from the study's Executive Steering Committee. An independent Data Monitoring Committee (DMC) performs confidential, continuing, critical, and unbiased evaluations of interim results and aggregate safety data reports to make recommendations to stop, modify, or continue the study. The DMC is led by a medical oncologist and includes a pulmonologist, two biostatisticians, two thoracic surgeons, and two radiation oncologists.

The CSP Human Rights Committee conducts site visits to enrollment sites to evaluate the consent and other study processes from a human rights perspective. The Site Monitoring, Auditing and Resource Team serves as the oversight quality assurance arm of CSP for Good Clinical Practice compliance as an independent arm of the study sponsor.

The study is registered with the United States Food and Drug Administration and received an Investigational Device Exemption on September 9, 2016 to evaluate the efficacy and safety of SBRT in a population of participants with operable stage I NSCLC.

Planned Interim Analyses

The interim monitoring plan uses an alpha-spending function approach with O'Brien-Fleming boundaries. As this is an event driven trial, interim analyses for efficacy, futility, and safety will be scheduled according to an expected 339 events during the study period (deaths from any cause). The first interim analysis is planned when one-third (113) of events have occurred; at that point, if the number of events for either treatment group exceeds 76, the interim monitoring boundaries will be crossed. The second interim analysis is planned when two thirds (226) of events will have occurred; at that point, if the number of events for either treatment group exceeds 132, the interim monitoring boundaries will be crossed. If the pre-specified interim monitoring boundaries are crossed at the first or second interim analysis, the study trial may be stopped early for efficacy or futility. A separate interim analysis for safety will evaluate the following: (1) differences in local, regional, and distant relapse, and (2) differences in severe treatment related toxicities.

The study's progress has been reviewed six times by the DMC (February 2017, February 2018, January 2019, January 2020, February 2022, and February 2023).

Current Trial Progress

The study was activated at six VA medical centers in April 2017 for a planned ramp-up phase. Enrollment proceeded well in several study sites and was slower in others. A recruitment

intervention developed by the QuinteT (Qualitative research integrated in Trials) research group was implemented in the form of a QuinteT Recruitment Intervention-Two (QRI-Two).[23] The QRI-Two identified issues with equipoise and difficulties among recruiters managing patient preferences; additional observations included variations in patient pathways between sites. A training event was held in 2018 to provide 'tips' for recruiters, and the informed consent forms were revised to better emphasize the purpose of the study. Following demonstration that barriers to randomizing participants between surgery and SBRT could be overcome, the study was expanded to nine sites in April 2018, and later to 16 sites in May 2019. All study sites have been credentialed for SBRT and are performing anatomic resections with video-assisted or robotic-assisted thoracoscopic surgery. Due to the SARS-CoV-2 pandemic, a temporary administrative hold was placed on recruitment on March 17, 2020 and lifted on August 26, 2020. As of July 5, 2023, 280 of 670 planned participants have been enrolled.

Discussion

The VALOR study is a part of the VA Lung Precision Oncology Program, which is a component of the Veterans Health Administration Precision Oncology Initiative. It provides Veterans access to new treatment options through relevant clinical trials that are aligned with a global strategy to translate discoveries into clinical care as appropriate.[24]

The results of this phase III study will clarify the role of SBRT for operable patients managed in a more contemporary era with more advanced diagnostic and treatment options. If OS is superior among patients randomized to SBRT, the findings may establish SBRT as the preferred treatment for stage I NSCLC. If OS is superior among patients randomized to anatomic resection, the findings will help primary care physicians, pulmonologists, thoracic surgeons, and radiation oncologists better understand that the perioperative risks of lung cancer surgery are justified whenever long-term survival is the primary goal.[25] If there is no difference in OS between the treatments, evidence-based guidelines may recommend both options and emphasize the importance of shared decisions during management discussions for the treatment of early-stage lung cancer.[26] Finally, carefully collected data on QOL and health state utilities in a balanced prospective cohort of participants enrolled in this study will facilitate more informed discussions in general about which treatment might be optimal for any given patient.

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TABLE 1 – Radiology assessments of lung cancer progression. These definitions, adapted from the ACOSOG-Z4099/RTOG-1021 phase III study, will be used to evaluate the secondary outcome measure of patterns of failure. Post-SBRT tumor responses will be separately scored using RECIST v1.1 for internal quality control purposes only.

Type of Relapse	Treatment Arm	Description (after resolution of treatment effects)
Local Failure		
Primary tumor failure (PTF)	SBRT	Appearance of residual tumor located within the extent of the primary targeted tumor
Marginal failure (MF)	Surgery	**Surgery**: Appearance of tumor ≤ 2 cm in any direction of the staple line of the structures immediately adjacent to the prior tumor site (chest wall / mediastinum / diaphragm / spine)
	SBRT	**SBRT**: Appearance of tumor ≤ 2 cm in any direction of the primary tumor or structures immediately adjacent to the primary tumor (lung / chest wall / mediastinum / diaphragm / spine)
Involved lobe failure (ILF)	Surgery	**Surgery**: Appearance of tumor > 2 cm in any direction of the staple line
	SBRT	**SBRT**: Appearance of tumor > 2 cm in any direction of the primary tumor
Post site/wound failure (PWF)	Surgery	Appearance of tumor at a port or incision site after surgery
Regional Failure		
Non-primary lobe failure (NLF)	SBRT / Surgery	Appearance of tumor within another Ipsilateral (non-primary) lobe.
Hilar nodal failure (HNF)	SBRT / Surgery	Appearance of tumor in Ipsilateral hilar lymph nodes
Ipsilateral mediastinal nodal failure (MNF)	SBRT / Surgery	Appearance of tumor in Ipsilateral mediastinal and/or subcarinal lymph nodes
Distant Failure		
Distant nodal failure (DNF)	SBRT / Surgery	Appearance of tumor in supraclavicular or contralateral lymph nodes
Distant metastatic failure (DMF)	SBRT / Surgery	Appearance of tumor deposits characteristic of NSCLC metastasis (chest wall other than incision sites or immediately adjacent to primary, mediastinal structures/diaphragm, malignant pleural effusion/pericardial effusion), contralateral lung and/or distant organs.

FIGURE 1 – Study Schema. The pathological nodal status (pN) is determined by surgical sampling and assigned by AJCC 7th edition staging criteria (pN_0 - no lymph node involvement, pN_1 – hilar lymph node involvement, pN_2 – ipsilateral mediastinal lymph node involvement, pN_3 – contralateral mediastinal and/or Ipsilateral supraclavicular lymph node involvement; cN_0 – no lymph node involvement by clinical assessment). *Surgical options include lobectomy or anatomic segmentectomy.

FIGURE 2 – Secondary endpoints. The twelve secondary endpoints are organized into two families with a hierarchical model to control for type I error that may result from multiple testing. Comparisons of secondary outcome measures between treatment arms in the second family will only occur if at least one outcome is significant in the first family.

TAKE HOME POINTS

- Study Question – What is the optimal treatment for early-stage non-small cell lung cancer (NSCLC)?

- Results – CSP #2005 (VALOR) is a phase III randomized clinical trial sponsored by the Veterans Affairs Cooperative Studies Program comparing the overall survival of patients with operable clinical stage I NSCLC treated with an anatomic lung resection lung resection or stereotactic body radiation therapy (SBRT). More than 40% of the planned 670 participants have been enrolled to date.

- Interpretations – The results of this study are expected to clarify the role of SBRT in lieu of surgery for operable stage I NSCLC and facilitate more informed discussions about these treatment options.