Joint Lung Cancer Trialist's Coalition

JoLT – Ca

A Randomized Phase III Study of Sublobar Resection (SR) versus Stereotactic Ablative Radiotherapy (SAbR) in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)

The STABLE-MATES Trial

Document History

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Acknowledgement

I have read and understand this Protocol. I agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined in the Protocol. I will provide copies and training to all individuals who assist in the conduct of this study.

Site Principal Investigator

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Site #: _____

Institution: _____

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_____

Signature: _____

Date: _____

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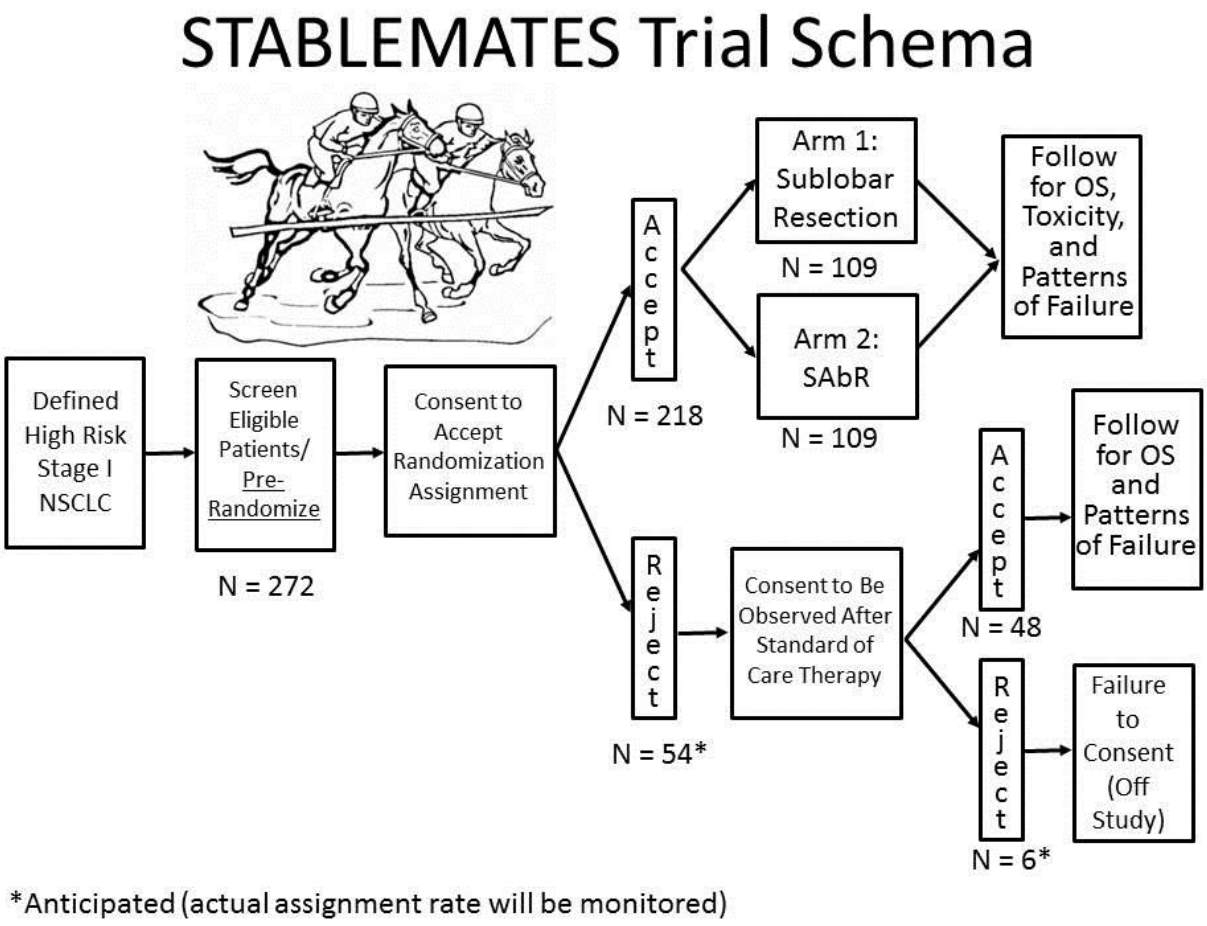
STABLE-MATES Trial Schema



*Anticipated (actual assignment rate will be monitored)

STUDY SUMMARY

Title	A Randomized Phase III Study of Sublobar Resection (SR) versus Stereotactic Ablative Radiotherapy (SAbR) in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC) – The STABLE-MATES Trial
Short Title	Sublobar Resection versus Stereotactic Ablative Radiotherapy in High Risk Operable Stage I NSCLC
Phase	Phase 3
Methodology	Pre-randomized trial- Patients will be screened and pre-randomized to either SR or SAbR. While discussions about the trial can be carried out prior to pre-randomization, informed consent will be obtained after patients are made aware of the pre-randomized assignment. Despite pre-randomization prior to consent, patients maintain their right to accept or decline any/all study activities. Only consenting patients will be allowed to participate in study activities, including observation after either randomized treatments or observation after standard of care treatment, while those declining consent will be managed by their physician(s) off study.
Study Duration	Anticipated duration of accrual is 5 years. Patients should continue to be followed a minimum of 5 years from end of therapy.
Study Center(s)	Multi-center
Objectives	Determine if SAbR improves survival over SR in High Risk Operable Stage I NSCLC
Number of Subjects	272
Diagnosis and Main Inclusion Criteria	High Risk Operable Patients with Stage I NSCLC
Study Product(s), Dose, Route, Regimen	Stereotactic Ablative Radiotherapy, 54 Gy in 3 fractions
Reference therapy	Sublobar Resection
Statistical Methodology	Pre-randomized, phase III trial comparing overall survival between SR and SAbR. The sample size is calculated with the 2-sided significance level of 0.05 and 80% statistical power using a 2-sample log rank test.

1.0 BACKGROUND AND RATIONALE

Disease Background

Resection of Stage I Non-Small Cell Lung Cancer (NSCLC) is currently the standard of care, with lobectomy or pneumonectomy leading to cure rates of 65-90% [1,2]. However, the population suffering from lung cancer often includes individuals with diminished cardiopulmonary function with considerable risks related to undergoing an operative procedure, the type of resection performed, as well as the post-operative course. Thus, individual patient risk-stratification can divide the Stage I NSCLC population into three categories:

(1) Standard-Risk Operable- potentially can tolerate lobectomy or pneumonectomy.

(2) High-Risk Operable- cannot tolerate pneumonectomy or lobectomy but potentially can tolerate sublobar resection (SR).

(3) Medically Inoperable- non-surgical candidates.

Sublobar resection via wedge resection or segmentectomy is the current standard of care in high risk operable patients [2,3]. With recent completion of the ACOSOG Z4032 Phase III trial (Fernando, PI) comparing sublobar resection with sublobar resection plus brachytherapy, the three year overall survival was found to be 71% in both arms [4]. Stereotactic Ablative Radiotherapy (SAbR) is now the standard of care amongst medically inoperable Stage I NSCLC patients, with the landmark RTOG 0236 study (Timmerman, PI) showing at 5-years the primary tumor failure (in-field/marginal) as only 7%, a 5-year overall survival (OS) of 40%, and a favorable long-term safety profile (ASTRO Abstract)[25]. Given the promising results and favorable toxicity profile amongst medically inoperable patients, extension to the high-risk operable patient population has been emerging within institutional and multicenter experiences.

Stereotactic Ablative Radiotherapy has been shown in single institution phase II and matched cohort studies to be effective at controlling primary early lung cancer. When comparing SAbR with wedge resection retrospectively, local recurrence (LR), locoregional recurrence (LocoR), and regional recurrence (RR) have been shown to be decreased with SAbR [5]. However, OS in this particular reference was found to be higher amongst patients who underwent wedge resection. This introduces one important limitation to retrospective data comparing the two procedures, as the majority of the patients who undergo SAbR are medically inoperable with expected poor outcomes. A second important issue when comparing the two treatment modalities is the variability in definitions of local control, local recurrence, and regional recurrence. When comparing similar patient populations with propensity score-matching, patients undergoing SAbR or video-assisted thoracoscopic surgery (VATS) lobectomy found SAbR to have higher rates of locoregional control [6].Recent pooled analysis of both the STARS and ROSEL randomized trials comparing SABR versus lobectomy have shown a significantly improved 3-year survival with SABR, giving further impetus for successful completion of a randomized trial [7]. Thus with similar patient populations, recent prospective as well as multiple retrospective series have shown that the 3-year survival amongst high-risk operable patients who undergo SAbR is as high as 95% (Table).

SAbR Data	Stage	3-Year Survival
SAbR- Dutch [8]	T1-T2N0	85%
SAbR-Japan(JCOG 0403) [9]	T1N0	76%
SAbR-Japan [10]	T1-T2N0	86%
SAbR-Japan [11]	T1-T2N0	80%
SAbR-Dutch [6]	T1-T2N0	80%
RTOG 0618[24]	T1-T3N0	77%
STARS/ROSELPooled[7]	T1-T2aN0	95%
Randomized Sublobar Data		
ACOSOG -Z4032 [4]	T1N0	71%
Non-Randomized Sublobar Data [12-14]	T1-T2N0	60-80%

Surgery is the standard of care, yet even with improvements in technique and technology, SAbR is clearly less toxic as it can safely treat medically inoperable patients. There is strong agreement in thoracic oncology circles among both surgeons and radiation oncologists that the two therapies should be formally compared in the context of high level testing. Conventionally designed phase III trials have been attempted both in the US and internationally, all failing to adequately accrue primarily due to patient refusal to accept a randomization that would assign them to very disparate therapies.

Pre-Randomization

Patient enrollment is one of the single most significant barriers to performing successful clinical trials, with the current financial climate only making their completion even more difficult. It is estimated that up to half of all phase III oncologic trials close due to inadequate accrual [15] with only 2-3% patient participation [16]. Analyses of causes for poor accrual have consistently shown that “patient dislike of randomization” and “loss of control over the decision making process” as being significant barriers to enrollment [16]. These concerns have been represented by lack of patient accrual in the previous three phase III randomized trials comparing SAbR versus either lobectomy or SR (ROSEL, STAR, ACOSOG Z4099/RTOG 1021). The ACOSOG Z4099/RTOG 1021 specifically selected high risk operable patients who could not tolerate a lobectomy, making it comparable to SAbR (a local only treatment). The trial earned considerable “buy-in” from the surgical community with over 60 sites opening the study. Unfortunately, it failed to accrue adequately and was closed. Comprehensive analysis of the accrual failure by the study team pointed squarely

toward patient refusal of randomization as the primary explanation for the accrual failure.

This leads to two problems which need to be addressed: (1) overcoming limitations in traditional clinical trial design; and (2) determining the efficacy and safety or SAbR versus SR (or any comparison of disparate therapies). When considering how to overcome poor patient accrual, we can look at the success of the National Surgical Adjuvant Breast and Bowel Project (NSABP). NSABP-B06 initially was opened with a traditional randomized trial design, with patients randomized to total mastectomy, breast conserving surgery, or breast conserving surgery plus adjuvant radiation. The trial was threatened for early closure due to difficulties with patient accrual with loss or preservation of the breast on the line [17]. When 94 NSABP investigators were mailed a questionnaire and asked why they chose not to enroll on the trial, investigators were concerned the “doctor-patient relationship would be effected by the randomization” along with concerns in obtaining informed consent with loss or preservation of the breast as a randomization [18]. The study was amended with a pre-randomization performed on all eligible patients prior to obtaining informed consent. Within a year after the study was amended, monthly patient accrual doubled and the trial not only was successfully completed but became one of the most important oncologic studies to have been performed [19].

Rationale

This trial is a re-design of ACOSOG Z4099/RTOG 1021, retaining that study’s PIs, with revision of the statistical methods to incorporate patient pre-randomization. In this design, all eligible patients are randomized to either SR or SAbR. Patients will be informed of their assigned treatment and then be allowed to accept or reject their assignment. At that point, informed consent will be obtained in order to move forward on trial comparing the two therapies. In the B-06 trial, 92% of patients consented accepted their assignment. All patients offered the protocol are recorded in site diaries which are intermittently reviewed by the study committee to monitor the percentage accepting the assignment. Based on the B-06 data and conservative estimation, we anticipate that up to 20% of patients consented will refuse treatment assignment and we will ask patients refusing the randomization assignment to be enrolled to the trial and followed for survival and recurrence only after standard of care therapies to ensure consistency with the standard arm on the randomized assignment. In this fashion, we expect that the trial will accrue and allow us to test the hypothesis.

At this time, given the failure of 3 traditional randomized controlled trials on 3 continents, we believe that this pre-randomization model is the only design that will allow successful accrual to a trial comparing such disparate therapies. Rather than abandon the potential to collect high level evidence for some of the most important comparisons in oncology, we believe this trial could be an example of how to conduct similar trials in the future. While traditional phase III trials randomizing after consent provide potentially “more clean” information for consideration, in cancer therapy they have mostly been used to compare more similar treatment such as two drugs used as primary therapy, or, conversely, to compare adjuvant (non-primary) therapies. Traditional randomized clinical trial designs have had a dismal record of either starting or completing comparisons of different primary therapies and should be strongly criticized for these shortcomings.

With successful completion of this trial, irrespective of the results, the two therapies will be better characterized so that oncologists can weigh patient factors in determining appropriate therapy. It will constitute high level prospective evidence when considering SR or SAbR to be used as a primary therapy in early stage lung cancer.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To test the hypothesis that overall survival rate in high risk operable patients with Stage I NSCLC is greater in patients who undergo SAbR as compared to standard sublobar resection (SR).

2.2 Primary Endpoints

2.2.1 Overall survival rate for Stage I NSCLC who undergo SR or SAbR. Overall survival will be measured from date of treatment initiation until death, 5 years from the end of treatment or closure of the study (whichever comes first).

2.3 Secondary Endpoints

2.3.1 Progression free survival for Stage I NSCLC who undergo SR or SAbR. Progression-free survival (PFS) is the time elapsed between treatment initiation and (1) any recurrence (local, regional or distant) or (2) death due to any cause.

2.3.2 Local and regional recurrence rates for Stage I NSCLC who undergo SR or SAbR. Time to local and regional recurrence is defined per section 10.0 and includes patients with failures of either the primary tumor and/or regional lymph nodes.

2.3.3 Distant recurrence rates for Stage I NSCLC who undergo SR or SAbR. Time to distant recurrence is defined per section 10.0 for patients with distant failure.

2.3.4 Assess toxicity using the Common Toxicity Criteria for Stage I NSCLC who undergo SR or SAbR.

3.0 SUBJECT ELIGIBILITY

Subjects must meet all of the inclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 Age ≥ 18 years.

3.1.2 ECOG/Zubrod performance status (PS) 0, 1, or 2.

3.1.3 Radiographic findings consistent with non-small cell lung cancer, including lesions with ground glass opacities with a solid component of 50% or greater. Those with ground glass opacities and <50% solid component will be excluded.

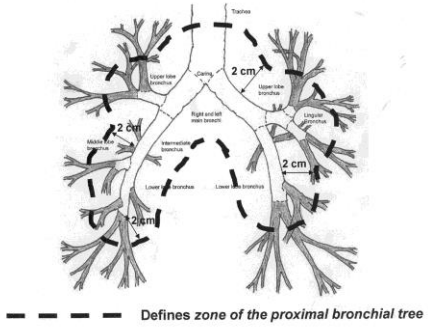
3.1.4 The primary tumor in the lung must be biopsy confirmed non-small cell lung cancer within 180 days prior to randomization.

3.1.5 Tumor ≤ 4 cm maximum diameter, including clinical stage IA and selected IB by PET/CT scan of the chest and upper abdomen performed within 180 days prior to randomization. Repeat imaging within 90 days prior to randomization is recommended for re-staging but is not required based on institutional norms.

3.1.6 All clinically suspicious mediastinal N1, N2, or N3 lymph nodes (> 1 cm short-axis dimension on CT scan and/or positive on PET scan) confirmed negative for involvement with NSCLC by one of the following methods: mediastinoscopy, anterior mediastinotomy, EUS/EBUS guided needle aspiration, CT-guided, video-assisted thoracoscopic or open lymph node biopsy within 180 days of randomization.

3.1.7 Tumor verified by a thoracic surgeon to be in a location that will permit sublobar resection.

3.1.8 Tumor located peripherally within the lung. NOTE: Peripheral is defined as not touching any surface within 2 cm of the proximal bronchial tree in all directions. See below. Patients with non-peripheral (central) tumors are NOT eligible.



3.1.9 No evidence of distant metastases.

3.1.10 Availability of pulmonary function tests (PFTs – spirometry, DLCO, +/- arterial blood gases) within 180 days prior to registration.

Patients with tracheotomy, etc, who are physically unable to perform PFTs (and therefore cannot be tested for the Major criteria in 3.1.11 below) are potentially still eligible if a study credentialed thoracic surgeon documents that the patient's health characteristics would otherwise have been acceptable for eligibility as a high risk but nonetheless operable patient (in particular be eligible for sublobar resection).

3.1.11 Patient at high-risk for surgery by meeting a minimum of one major criteria or two minor criteria as described below:

Major Criteria

- FEV1 ≤ 50% predicted (pre-bronchodilator value)
- DLCO ≤ 50% predicted (pre-bronchodilator value)

Minor Criteria

- Age ≥75
- FEV1 51-60% predicted (pre-bronchodilator value)
- DLCO 51-60% predicted (pre-bronchodilator value)
- Pulmonary hypertension (defined as a pulmonary artery systolic pressure greater than 40mm Hg) as estimated by echocardiography or right heart catheterization
- Study credentialed thoracic surgeon believes the patient is potentially operable but that a lobectomy or pneumonectomy would be poorly tolerated by the patient for tangible or intangible reasons. The belief must be declared and documented in the medical record prior to randomization.
- Poor left ventricular function (defined as an ejection fraction of 40% or less)
- Resting or Exercise Arterial pO2 ≤ 55 mm Hg or SpO2 ≤ 88%
- pCO2 > 45 mm Hg
- Modified Medical Research Council (MMRC) Dyspnea Scale ≥ 3.

Grade	Description
0	No breathlessness except with strenuous exercise
1	Breathlessness when hurrying on the level or walking up a slight hill
2	Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level
3	Stops for breath after walking about 100 yards or a few minutes on the level

4	Too breathless to leave the house or breathless when dressing or undressing

3.1.12 No prior intra-thoracic radiation therapy for previously identified intra-thoracic primary tumor (e.g. previous lung cancer) on the ipsilateral side. NOTE: Previous radiotherapy as part of treatment for head and neck, breast, or other non-thoracic cancer is permitted to the ipsilateral side so long as possible radiation fields would not overlap. NOTE: Radiotherapy to the contralateral lung is allowed so long as it was completed more than 3 years prior to randomization and there is no overlap of radiation fields.

3.1.13 Previous chemotherapy, radiotherapy, or surgical resection specifically for the lung cancer being treated on this protocol is NOT permitted.

3.1.14 No prior lung resection on the ipsilateral side.

3.1.15 Non-pregnant and non-lactating. Women of child-bearing potential must have a negative urine or serum pregnancy test prior to registration. Peri-menopausal women must be amenorrheic $\geq$ 12 months prior to registration to be considered not of childbearing potential.

3.1.16 No prior invasive malignancy, unless disease-free for ≥ 3 years prior to registration (exceptions: non-melanoma skin cancer, in-situ cancers).

3.1.17 Ability to understand and sign a written informed consent.

4.0 PATIENT REGISTRATION/RANDOMIZATION

All patients who are screened and found eligible by the above criteria will be entered into a screening log at the enrolling site and pre-randomized prior to consent to either SR or SAbR.

Clinical information about each treatment arm will be conveyed to the patient at consultation and they will be informed of which treatment arm they have been assigned from the pre-randomization. If the patient wishes to consent to accept the pre-randomization assignment, they will sign the informed consent document and then go on to receive either SR or SAbR with follow-up per the study calendar (patterns of failure, progression free and overall survival and toxicity). If the patient rejects (refuses) to consent to the pre-randomization assignment, they will then be offered the opportunity to be followed on the trial after standard of care treatment per the study calendar for progression free and overall survival. Patients rejecting (refusing) consent for any study activities will not be followed (off study).

5.0 STUDY PROCEDURES

5.1 Sublobar Resection

For patients randomized to Arm 1, a wedge resection or anatomical segmentectomy will be performed. Thoracotomy or VATS approach is allowed. A technically successful sublobar resection will be defined as either a segmentectomy or a wide wedge resection with at least a 1 cm margin from the tumor to the staple line. Brachytherapy is not allowed after SR. **If a wedge resection alone is performed, intraoperative pathology consultation should be obtained as part of an effort to obtain and confirm at least a 1 cm margin from the tumor to the staple line and documented in the operative report.** While it may not always to be possible to achieve a minimum 1 cm margin, the surgeon should make strong effort to meet this standard. Lymph node sampling is highly recommended but not required.

5.1.1 Touch Prep for Staple Line

It is highly recommended that a touch prep of the specimen be performed using the run-across method described by Sawabata et al [20]. The cytological examination should be performed before the specimen is cut for histological examination to prevent malignant cell contamination. In those procedures where a frozen section is to be performed to confirm cancer, the touch prep should be performed first for the same reason. A glass slide should be run across the entire staple margin **of the specimen after removal from the thoracic cavity** at least 3 times. The slide should be run over the specimen after it is removed from the patient but before the specimen is cut by the pathologist. The slide does not need to touch the remaining non-resected lung. This slide containing the extracted specimen should be spread on another slide and fixed for cytological examination. A positive margin will be defined as at least 3 malignant cells or clustered malignant cells on the glass slide. **NOTE: Documentation of the staple line touch prep should be included in the final operative and pathology reports, however an intraoperative determination of the staple-line cytology is not required.**

5.2 Stereotactic Ablative Radiotherapy (SAbR)

5.2.1 Stereotactic Targeting and Treatment

SAbR has now been formally defined and described in a published guideline from the American College of Radiology and American Society for Therapeutic Radiology and Oncology. [104] This protocol will respect that guideline. The term stereotactic for the purposes of this protocol implies the targeting, planning, and directing of therapy using beams of radiation along any trajectory in 3-D space toward a target of known 3-D coordinates. The coordinate system is defined by reliable “fiducials”. A “fiducial” may be external or internal to the patient’s body. External fiducials may relate to a frame or treatment device. Internal fiducials may be implanted markers or reliably identified anatomy including the tumor itself (e.g., acquiring tomographic views of the tumor simultaneously with the treatment). In all cases, the relationship between the fiducial and the actual tumor position should be reliably understood for both planning and treatment. This differs from conventional radiation therapy, in which therapy is directed toward less-than-reliable skin marks or bony landmarks that may not have a well described relationship in space compared to the soft tissue tumor target. This protocol will require treatments to be conducted with the use of a fixed 3-D coordinate system defined by fiducials. The coordinate system defined by the fiducials should be directly related to the radiation-producing device (e.g., couch and gantry) in a reproducible and secure fashion. Capability should exist to define the position of targets within the patient according to this same 3-D coordinate system. As such, the patient is set up for each treatment with the intention of directing the radiation toward an isocenter or target according to the known 3-

D coordinates as determined in the process of treatment planning. Metallic “seeds” placed within or near the tumor will be allowed to constitute a fiducial provided the methods are validated and a plan is in place to identify seed migration (e.g., redundant seeds placed).

5.2.2 Dose Fractionation

Patients will receive 3 fractions of radiation. The dose for all patients will be 18 Gy per fraction to the prescription line at the edge of the PTV (total dose = 54 Gy). All treatment must be completed within 16 days. The time between fractions is at the discretion of the investigator, but a minimum of 40 hours and a maximum of 8 days should separate each treatment.

5.2.3 Premedications

Although not mandatory, it is recommended that patients receive corticosteroid premedication (e.g., Dexamethasone 4 mg p.o. in a single dose, or equivalent) 15-60 minutes before each of the three treatments for the intended purpose of modulating immediate pulmonary inflammatory effects. Analgesic or sedative premedication to avoid general discomfort during long treatment durations also is recommended when appropriate.

5.3 Technical Factors

5.3.1 Physical Factors and Treatment Platforms

Only photon (x-ray) beams produced by linear accelerators with photon energies of 4-10 MV will be allowed. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed. Photon beam energies > 10 MV but < 15 MV will be allowed only for a limited number (≤ 50% of all beams or all beam angles) beams that must travel more than a cumulative distance of 10 cm through soft tissue (not lung) to reach the treated tumor OR a shorter distance if the tumor abuts the chest wall (i.e., to spare skin dose).

Most commercially available photon producing treatment units are allowed except the exclusions noted above. As such, conventional linear accelerators, specialized linear accelerators with image guidance (e.g., Novalis, Trilogy, Synergy, Artiste, TruBeam, Agility, Versa HD, Vero) are allowed. These units can be used with conformal dose delivery or IMRT. Specialized dose painting accelerators (e.g., Cyberknife, or Tomotherapy) are allowed provided they meet the technical specifications of the protocol and are used in a fashion that passes the credentialing required by the protocol.

5.3.2 Minimum Field Aperture (Field Size) Dimension

Because of uncertainties in beam commissioning resulting from electronic disequilibrium within small beam apertures, an equivalent square field dimension of 2.5 cm is required for any field used for treatment delivery for sites using standard 3-D conformal techniques where nearly all of the PTV is encompassed for each beam. Smaller apertures should have been “commissioned” as part of acceptance testing and for beam modeling used in treatment planning for the particular linac. It is understood that this may exceed the technical requirements for small lesions [< 1.5 cm axial gross tumor volume (GTV) dimension or < 1.0 cm craniocaudal GTV dimension]. In such cases, the prescription dose is still prescribed to the edge of the defined planning treatment volume (PTV). For sites using dose painting including IMRT techniques (e.g., Cyberknife, Tomotherapy, etc.) where by design the entire PTV is not encompassed for each beam, smaller beam apertures are allowed.

5.3.3 Dose Verification at Treatment

Personal dosimeter measurements (e.g., diode, TLD) may be obtained for surface dose verification for accessible beams as per institutional preference.

5.3.4 The Use of Intensity Modulated Radiation Therapy (IMRT) Using Multileaf Collimation

The protocol allows for IMRT provided the site is credentialed for IMRT and SAbR. However, SAbR is, in general, a 3-D conformal treatment. Furthermore, IMRT can result in dosimetric inaccuracies especially in circumstances where tumor motion is either unknown or not properly accounted. Some platforms inherently use IMRT and must pass credentialing where motion is incorporated correctly (e.g., Tomotherapy). When using other platforms, IMRT is generally discouraged. When required for successful compliance, IMRT should only be utilized if tumor motion is less than 5 mm, OR if motion management inherently diminishes motion effects (e.g., gating, breath hold, or tracking) below the 5mm level.

5.4 Localization, Simulation, and Immobilization

5.4.1 Patient Positioning

Patients will be positioned in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be used, including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients' external contours) with reference to the stereotactic coordinate system. Patient immobilization must be reliable enough to insure that the gross tumor volume (GTV) does not deviate beyond the confines of the planning treatment volume (PTV) with any significant probability (i.e., < 5%).

5.4.2 Assessment of the Magnitude of Internal Organ Motion

Special considerations must be made to account for the effect of internal organ motion (e.g., breathing) on target positioning and reproducibility. As a first step, it is required that each site quantify the specific motion of a target so as to determine if management strategies listed in the next section are required to meet protocol guidelines. The GTV to PTV expansion limits, as defined below, are no greater than 0.5 cm in the axial plane and 1.0 cm in the craniocaudal plane. If tumor motion combined with set-up error causes the PTV to be greater than the GTV beyond these limits, then a motion management strategy (or plan to reduce setup error) must be employed with validation of success. Patient should be instructed to be in normal free breathing at time of initial tumor motion assessment. Deep inspiration or expiration breath hold is not allowed for initial tumor motion assessment as such assessment generally overestimates free breathing tumor motion. Options for motion assessment included real time fluoroscopy, 4-D CT scanning, or other methods approved by the study team.

5.4.3 Management of Effects of Internal Organ Motion

In some tumor locations, assessed tumor motion measurement indicates that tumor motion would exceed the required small tumor expansions per this protocol (resulting in marginal miss or excessive volume of irradiation) unless a motion management strategy is employed. Acceptable maneuvers for motion management include reliable abdominal compression, accelerator beam gating with the respiratory cycle, tumor tracking, and active breath-holding techniques or other methods approved by the study committee as

part of credentialling. Internal organ management maneuvers must be reliable enough to insure that the GTV does not deviate beyond the confines of the PTV with any significant probability (i.e., < 5%).

5.4.4 Localization

Isocenter or reference point port localization films (anterior/posterior and lateral) should be obtained at each treatment on the treatment unit (or patients should undergo a tomographic imaging study on the linear accelerator couch, if available) immediately before treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields. All IGRT systems must be checked daily to guarantee coincidence between the imaging coordinate system and the treatment coordinate system. This test is required by the AAPM Task Group 142 report [130] and is described in detail in both the ASTRO/ACR practice guideline on SBRT available at:

http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/ro/stereo_body_radiation and the ACR Technical Standard on IGRT available at: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/med_phys/monitor_IGRT.

This test is particularly important when the treatment equipment is not equipped with any device that allows direct visualization of anatomical structures using the treatment beam. For example, this test must be performed routinely for the CyberKnife, Tomotherapy units as well as any BrainLab equipment that does not include an electronic portal imaging device (EPID) that intercepts the treatment beam.

5.5 Treatment Planning/Target Volumes

5.5.1 Image Acquisition

Computed tomography will be the primary image platform for targeting and treatment planning. The planning CT scans must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting and must be done with IV contrast unless the patient has allergic problems with contrast or has renal insufficiency. Contrast will allow better distinction between tumor and adjacent vessels or atelectasis. Axial acquisitions with gantry 0 degrees will be required with spacing ≤ 3.0 mm between scans. Images will be transferred to the treatment planning computers via direct lines, disc, or tape.

The target lesion will be outlined by an appropriately trained physician and designated the gross tumor volume. The target will generally be drawn using CT pulmonary windows; however, soft tissue windows with contrast may be used to avoid inclusion of adjacent vessels, atelectasis, or mediastinal or chest wall structures within the GTV. **This target will not be enlarged whatsoever for prophylactic treatment (including no "margin" for presumed microscopic extension); rather, include only abnormal CT signal consistent with gross tumor (i.e., the GTV and the clinical target volume [CTV] are identical)**. An additional 0.5 cm in the axial plane and 1.0 cm in the longitudinal plane (craniocaudal) will be added to the GTV to constitute the PTV.

As an alternative, sites equipped with 4-D CT scanning equipment may generate an Internal Target Volume (ITV) using the inspiration and expiration reconstructions or maximum intensity projections (MIP) as appropriate. Sites should be aware that the MIP reconstruction may erroneously define an ITV in cases of significant irregular breathing or when tumors abut soft tissue structures (e.g., the diaphragm). The 4-D scan acquired for planning, however, should be obtained after initial assessment of tumor motion

confirming that the tumor motion will be no greater than 0.5 cm in the axial plane and 1.0 cm in the craniocaudal plane. In general, an ITV should NOT be defined by the merger of a deep inspiration CT scan and a deep expiration CT scan as such would typically overestimate tumor motion. The ITV, then, is generated using a CT dataset where motion control maneuvers are already successfully employed. This ITV can be expanded by the institution's geometric set-up uncertainty (e.g., 4-5 mm) to generate the PTV.

As an example of this process, the University of Texas Southwestern employs the following steps to assess motion, manage motion, acquire image datasets, and generated targets. First a motion study is done (using fluoroscopy) to determine if the GTV is moving more than 1.0 cm. If it is, abdominal compression is applied with coaching (urging the patient not to "push back" against the abdominal plate) until the GTV moves less than 1.0 cm (verified again on fluoroscopy). Then, with compression/coaching applied when necessary, a 4-D CT is done. The 4-D CT allows the site to generate an ITV using either by a reconstructed MIP or with the expiratory/inspiratory phase scans, but this is a motion managed ITV (not necessarily free breathing). The site confirms that this motion managed ITV generated by the 4DCT (as opposed to the fluoroscopy assessment) has limited GTV motion per protocol requirements. As the site treats in a stereotactic body frame, the validated institutional setup error is small. The site compares the mid amplitude GTV expanded by 0.5-1.0 cm PTV as required by protocol requirements to the ITV plus setup error to insure they are consistent. The resulting PTV is small yet contains tumor motion and all of our setup errors.

5.5.2 Dosimetry

Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are preferable. Typically, ≥ 10 beams of radiation will be used with roughly equal weighting. Generally, more beams are used for larger lesion sizes. When static beams are used, a minimum of seven non-opposing beams should be used. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized. For this protocol, when using a gantry mounted linear accelerator, the isocenter is defined as the common point of gantry and couch rotation for the treatment unit. For other types of treatment units (e.g., tomotherapy or CyberKnife), a reference point in space that is typically positioned at the center of the target is used instead of a mechanical isocenter. For non-IMRT or dose painting techniques, the conformal field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). The only exception will be when observing the minimum field dimension of 2.5 cm when treating small lesions (see above). As such, prescription lines covering the PTV will typically be the 60-90% of maximum line (rather than 95-100% as is common with conventional radiotherapy); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. The stereotactic reference point (corresponding to the mechanical isocenter for gantry mounted treatment units) will be determined from system fiducials (or directly from the tumor) and translated to the treatment record.

The treatment dose plan will be made up of multiple static beams or arcs as described above. For both IMRT and CyberKnife treatments, the apertures are determined by inverse treatment planning. In both cases, the end result is a very large number of beam

apertures that do not necessarily include any particular single point in space. That is, the individual beams are not "isocentric." However, as stated above, whenever possible, IMRT plans should be avoided. The resulting plan should be initially normalized to a defined point corresponding closely to the center-of-mass of the PTV (COM_{PTV}). This normalization is used to select the isodose surface surrounding the target (see below where the exact coverage is stated as 95% of the PTV). Typically, in the case of the gantry mounted treatment units, this point will be the isocenter of the beam rotation; however, it is not a protocol requirement for this point to be the isocenter. For treatment units that do not have a mechanical isocenter, the center-of-mass of the PTV should be used. Regardless of the treatment unit type, the point identified as COM_{PTV} must have defined stereotactic coordinates and must receive 100% of the normalized dose. Because the beam apertures for the 3D-CRT approach coincide nearly directly with the edge of the PTV (little or no added margin), the external border of the PTV will be covered by a lower isodose surface than usually used in conventional radiotherapy planning, typically around 80% but ranging from 60-90%. For the treatment techniques that use inverse planning algorithms, this same isodose coverage must be achieved. The prescription dose of 54 Gy in 3 fractions will be delivered to the margin of the PTV (as defined below) and fulfill the requirements below. As such, a "hotspot" will exist within the PTV centrally at the COM_{PTV} with a magnitude of 54 Gy times the reciprocal of the chosen prescription isodose line (i.e., 60-90%).

For purposes of dose planning and calculation of monitor units for actual treatment, approved corrections for tissue heterogeneity must be used. Examples of appropriate tissue density heterogeneity correction algorithms include properly commissioned superposition/convolution (collapsed cone), AAA, and Monte Carlo. Simple pencil beam and Clarkson algorithms that account for attenuation but not scatter will not be allowed.

Successful treatment planning will require accomplishment of all of the following criteria:

1. **Normalization**

   The treatment plan should be normalized such that 100% corresponds to the center of mass of the PTV (COM_{PTV}). This point will typically also correspond (but is not required to correspond) to the isocenter of the treatment beams for gantry mounted devices.

2. **Prescription Isodose Surface Coverage**

   The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface of 54 Gy and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose (i.e., 48.6 Gy).

3. **Target Dose Heterogeneity**

   The prescription isodose surface selected in number 2 (above) must be ≥ 60% of the dose at the center of mass of the PTV (COM_{PTV}) and ≤ 90% of the dose at the center of mass of the PTV (COM_{PTV}). The COM_{PTV} corresponds to the normalization point (100%) of the plan as noted in number 1 above.

4. **High Dose Spillage**

a) Location: Any dose > 105% of the prescription dose should occur primarily within the PTV itself and not within the normal tissues outside the PTV. Therefore, the cumulative volume of all tissue outside the PTV receiving a dose > 105% of prescription dose should be no more than 15% of the size of the PTV volume.

b) Volume: Conformality of PTV coverage will be judged such that the ratio of the volume of the prescription isodose meeting criteria 1 through 4 to the volume of the PTV is ideally < 1.2 (see table below). These criteria will not be required to be met in treating very small tumors (< 1.5 cm axial GTV dimension or < 1.0 cm craniocaudal GTV dimension) in which the required minimum field size of 2.5 cm results in the inability to meet a conformality ratio of 1.2.

5. Intermediate Dose Spillage

The falloff gradient beyond the PTV extending into normal tissue structures must be rapid in all directions and meet the following criteria:

1. Location: The maximum total dose over all 3 fractions in Gray (Gy) to any point 2 cm or greater away from the PTV in any direction must be no greater than D_{2cm} where D_{2cm} is given by Table below in section 5.3.
2. Volume: The ratio of the volume of the 27 Gy isodose volume (50% of the prescription dose) to the volume of the PTV must be no greater than $R_{50\%}$ where $R_{50\%}$ is given by the table below.

5.6 Adherence to Critical Organ Dose-Volume Limits

Acceptable Spillage Guidelines

Ratio of Prescription Isodose Volume to the PTV		Ratio of 27 Gy Isodose Volume to the PTV, $R_{50\%}$		Maximum Dose at 2 cm from PTV in any direction as % of prescribed dose (PD). D_{2cm} (Gy) = % x PD		Percent of Lung receiving 20 Gy total or more, V_{20} (%)		PTV Volume (cc)
Deviation		Deviation		Deviation		Deviation		
none	acceptable	none	acceptable	none	acceptable	none	acceptable	
<1.2	<1.5	<5.9	<7.5	<50.0	<57.0	<10	<15	1.8
<1.2	<1.5	<5.5	<6.5	<50.0	<57.0	<10	<15	3.8
<1.2	<1.5	<5.1	<6.0	<50.0	<58.0	<10	<15	7.4
<1.2	<1.5	<4.7	<5.8	<50.0	<58.0	<10	<15	13.2
<1.2	<1.5	<4.5	<5.5	<54.0	<63.0	<10	<15	22.0
<1.2	<1.5	<4.3	<5.3	<58.0	<68.0	<10	<15	34.0
<1.2	<1.5	<4.0	<5.0	<62.0	<77.0	<10	<15	50.0
<1.2	<1.5	<3.5	<4.8	<66.0	<86.0	<10	<15	70.0
<1.2	<1.5	<3.3	<4.4	<70.0	<89.0	<10	<15	95.0
<1.2	<1.5	<3.1	<4.0	<73.0	<91.0	<10	<15	126.0
<1.2	<1.5	<2.9	<3.7	<77.0	<94.0	<10	<15	163.0

Note 1: For values of PTV dimension or volume not specified, linear interpolation between table entries is required.

Note 2: Institutions are encouraged to stay within the values listed as “none” in the table above so that the treatment plan is considered to be per protocol. It is recognized that some treatment planning situations might be more challenging and fall outside these limits, so staying within the values listed as “acceptable” is also permitted. Protocol deviations greater than listed here as “acceptable” will be classified as “unacceptable” for protocol compliance.

6.0 ADHERENCE TO CRITICAL ORGAN DOSE-VOLUME LIMITS

The following table lists dose limits to a point or volume within several critical organs/tissues. **For the spinal cord, these are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation**. For the non-spinal cord tissues, acceptable deviation allows a maximum point dose no more than 105% of the prescription dose (56.7 Gy as a total dose or 18.9 Gy per fraction) while fully respecting the defined volume constraint (for serial tissues) OR exceeding the parallel tissue critical volume dose maximum by no more than 5%. Unacceptable deviation exceeds the volume constraint for serial tissues, exceeds the maximum point dose for serial tissues by more than 105% of the prescription dose, or exceeds the parallel tissue critical volume dose maximum by more than 5%.

The normal tissue constraints listed in the following table list **total dose over 3 fractions** as well as per fraction. Participating centers are encouraged to observe prudent

treatment planning principles in avoiding unnecessary radiation exposure to critical normal structures irrespective of these limits.

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)**	Endpoint (≥ Grade 3)
Spinal Cord and medulla	<0.35 cc	15.9 Gy (5.3 Gy/fx)	22.5 Gy (7.5 Gy/fx)	Myelitis
Esophagus*	<5 cc	17.7 Gy (5.9 Gy/fx)	25.2 Gy (8.4 Gy/fx)	Stenosis/fistula
Brachial Plexus	<3 cc	22 Gy (7.3 Gy/fx)	26 Gy (8.7 Gy/fx)	Neuropathy
Heart/Pericardium	<15 cc	24 Gy (8 Gy/fx)	30 Gy (10 Gy/fx)	Pericarditis
Great vessels	<10 cc	39 Gy (13 Gy/fx)	45 Gy (15 Gy/fx)	Aneurysm
Trachea and Large Bronchus*	<5 cc	25.8 Gy (8.6 Gy/fx)	30 Gy (10 Gy/fx)	Stenosis/fistula
Rib	<5 cc	40 Gy (13.3 Gy/fx)	50 Gy (16.7 Gy/fx)	Pain or fracture
Skin	<10 cc	31 Gy (10.3 Gy/fx)	33 Gy (11 Gy/fx)	Ulceration
Stomach	<5 cc	22.5 Gy (7.5 Gy/fx)	30 Gy (10 Gy/fx)	Ulceration/fistula
Colon*	<20 cc	24 Gy (8 Gy/fx)	34.5 Gy (11.5 Gy/fx)	Colitis/fistula
Parallel Tissue	**Critical Volume**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥ Grade 3)**
Lung (Right & Left)	1500 cc	10.5 Gy (3.5 Gy/fx)		Basic lung function
Lung (Right & Left)	1000 cc	11.4 Gy (3.8 Gy/fx)		Pneumonitis
Liver	700 cc	17.1 Gy (5.7 Gy/fx)		Basic liver function
Renal cortex (Right & Left)	200 cc	15 Gy (5 Gy/fx)		Basic renal function

* Avoid circumferential irradiation
** A “point” is defined as a volume of 0.035 cc or less

6.1 Naming and Contouring of Normal Tissue Structures

Spinal Cord

The spinal cord will be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.
NOTE: For the spinal cord, these are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation.

Esophagus

The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.

Brachial Plexus

The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamina on the involved side from around C5 to T2. However, for the purposes of this protocol, only the major trunks of the brachial plexus will be contoured. The brachial plexus will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib. If the PTV is more than 10 cm away from the brachial plexus, this structure need not be contoured.

Heart

The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aorto-pulmonary window) and extend inferiorly to the apex of the heart.

Trachea and Proximal Bronchial Tree

The trachea and proximal bronchial tree will be contoured as two separate structures using mediastinal windows on CT to correspond to the mucosal, submucosa and cartilage rings and airway channels associated with these structures. For this purpose, the trachea will be divided into two sections: the proximal trachea and the distal 2 cm of trachea. The proximal trachea will be contoured as one structure, and the distal 2 cm of trachea will be included in the structure identified as proximal bronchial tree. Differentiating these structures in this fashion will facilitate the eligibility requirement for excluding patients with tumors within 2 cm of the proximal bronchial tree.

Proximal Trachea

Contouring of the proximal trachea should begin at least 10 cm superior to the extent of the PTV or 5 cm superior to the carina (whichever is more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree.

Proximal Bronchial Tree

The proximal bronchial tree will include the most inferior 2 cm of distal trachea and the proximal airways on both sides as indicated in the diagram in above. The following airways will be included according to standard anatomic relationships: the distal 2 cm of trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation.

Whole Lung

Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. All inflated and collapsed lung should be contoured; however, gross tumor (GTV) and trachea/ipsilateral bronchus as defined above should not be included in this structure.

External Body Contour

The limits of all body tissues at the external air/tissue interface on each axial slice will be contoured as a single structure to be used in defining additional contours and calculating dosimetric parameters for planning and QA.

PTV + 2 cm

As part of the QA requirements for "low dose spillage" listed above, a maximum dose to any point 2 cm away in any direction is to be determined. To facilitate this QA requirement, an artificial structure 2 cm larger in all directions from the PTV is required. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning. If possible this structure should be constructed as a single contour that is 2 cm larger than the PTV.

External Body Contour Minus PTV + 2 cm

Created by taking the External Body Contour and subtracting all the tissue within the PTV + 2 cm contours. This contour will be used to assess the maximum dose in the plan greater than 2 cm from the PTV in any direction (D2cm) which is used in evaluating the dose gradients outside the PTV target (dose spillage).

Proximal Bronchial Tree + 2 cm

As part of adhering to the ineligibility requirements for not enrolling patients with tumors in the zone of the proximal bronchial tree depicted above, it is convenient to define an artificial structure 2 cm larger in all directions from the proximal bronchial tree. If the GTV falls within this artificial structure, the patient should not be treated with the protocol therapy.

Skin

The skin will be defined as the outer 0.5 cm of the body surface. As such it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The External Body Contour can be used to auto-generate this structure (the annulus created by subtracting 0.5 cm from external body contour to the skin surface). The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations (e.g., the scalp on the top of the head).

Rib

Ribs within 5 cm of the PTV should be contoured by outlining the bone and marrow. Typically, several portions of adjacent ribs will be contoured as one structure. Adjacent ribs, however, should not be contoured in a contiguous fashion (i.e., do not include the inter-costal space as part of the ribs).

Other Structures

The constraints tables above contain other structures. These are required if the structure is within 10 cm of the PTV.

6.2 Planning Priorities

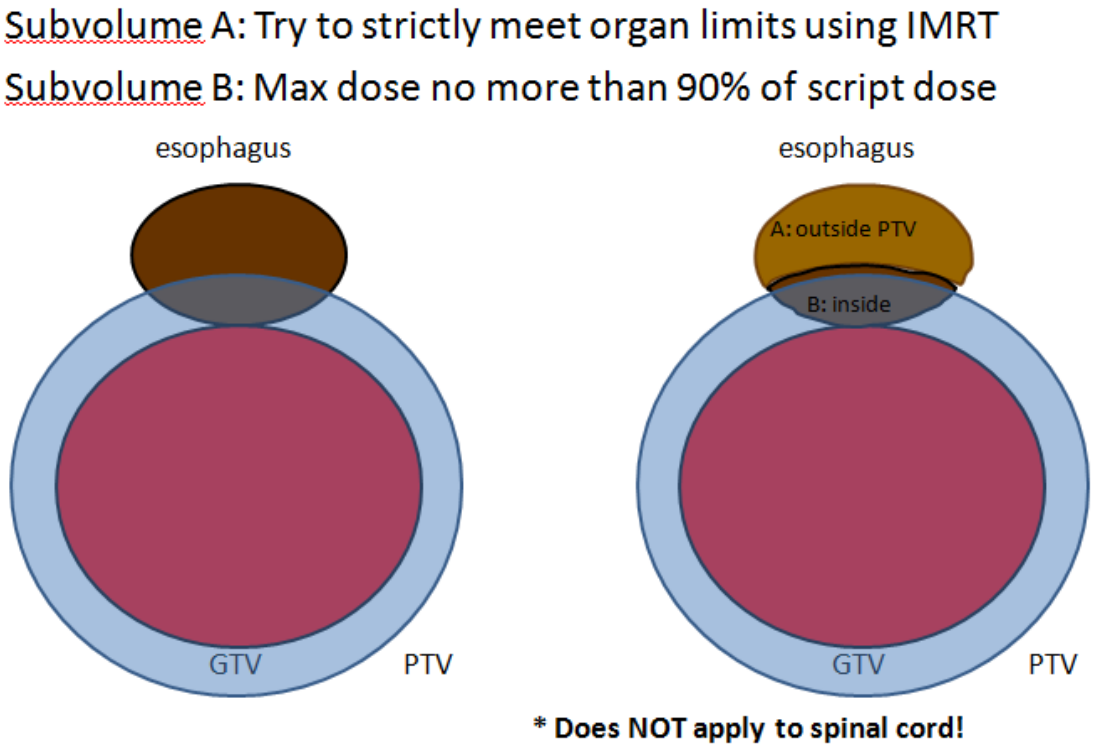
Successful treatment planning goals are listed above. In general, attempts should be made to successfully satisfy all of the goals without deviation. In some circumstances, improvements can be made to the dosimetry plan beyond simply meeting the specified goals. In other circumstances, clinicians are faced with the prospect of not ideally meeting one or more of the goals (i.e., accepting an acceptable deviation). In this section,

we provide priorities in which a most ideal plan for protocol purposes is realized. Suggested priority of planning goals in order of importance is:

1. Respect spinal cord dose constraints.
2. Meet dose “compactness” constraints including the high dose conformality constraint, D2cm, and R50
3. Meet organ constraints other than spinal cord.

The organ constraints are last in priority (except for spinal cord tolerance), because they are the least validated. The “essence” of a stereotactic plan is captured mostly in the dose compactness justifying their higher priority. As an example in a case where not all goals can be met, it would be suggested to meet dose compactness goals without deviation even at the expense of a non-spinal cord normal tissue having acceptable deviation. Unacceptable deviations should be avoided in all cases. Again, these are suggested planning priorities and clinicians must use their judgment and experience in actual treatment given the variability of patient presentation and tolerance.

As an example, in some cases a target abuts a normal tissue structure with an assigned constraint (e.g., the target abuts the esophagus as in figure below). Obviously, it would be impossible to utilize the required expansions, treat to 54 Gy PTV dose, and also meet the normal tissues maximum dose constraint. With the exception of the spinal cord, the protocol allows an “acceptable” deviation such that the abutting normal tissue is allowed a maximum point dose of 105% of the prescription dose; however, the volume constraint must still be respected. As such, the dosimetry might be manipulated by falloff dose polarization so that the compactness criteria are met with an “acceptable” deviation of normal tissue constraints.



6.3 Treatment Interruptions and Adverse Event Management Guidelines

In general, the need for treatment interruptions is rare in patients receiving SAbR. Interruptions should be avoided by preventative medical measures and nutritional, psychological, and emotional counseling. Treatment breaks, including indications, must be clearly documented in the treatment record.

Pneumonitis

Radiation pneumonitis is a subacute (weeks to months from treatment) inflammation of the end bronchioles and alveoli. **Note:** It is very important that a Radiation Oncologist participate in the care of the patient, as the clinical picture may be very similar to acute bacterial pneumonia, with fatigue, fever, shortness of breath, nonproductive cough, and a pulmonary infiltrate on chest x-ray. The infiltrate on chest x-ray should include the area treated to high dose, but may extend outside of these regions. The infiltrates may be characteristically “geometric” corresponding to the radiation portal, but may also be ill defined.

Patients reporting symptoms as above will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with nonsteroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary toilet. Supra- and concurrent infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised patients.

It is unlikely that symptomatic pneumonitis will occur during the weeks radiation is actually delivered to the patients. However, if a patient experiences pneumonitis before completing therapy, therapy will be put on hold until symptoms resolve.

Bronchial Injury (e.g., bronchial obstruction; bronchial stricture; bronchopleural fistula)

Bronchial injury with subsequent focal collapse of lung may impair overall pulmonary status. It also makes further assessment of tumor response more difficult as the collapsed lung approximates the treated tumor. Because atelectatic lung and tumor have similar imaging characteristics, radiology reports will often describe the overall process as progressive disease while the actual tumor may be stable or shrinking. Investigators are referred to the strict criteria for progressive disease to avoid such mischaracterization.

The consequences of bronchial toxicity, e.g., cough, dyspnea, hypoxia, impairment of pulmonary function test parameters, pleural effusion or pleuritic pain (associated with collapse), will all be graded and reported on adverse event forms.

Chest Wall Pain and/or Fracture (Rib)

When treating lesions about the chest wall, some patients will experience chest wall pain either as a result of intercostal neuropathy or rib fracture. Focal radiation induced osteoporosis can result in both occult and obvious rib fractures generally propagated by severe coughing/sneezing episodes or chest wall trauma (e.g., bumping into a kitchen cabinet). The pain typically occurs several months after treatment and may last several more months.

Changes in Pulmonary Function Tests (e.g., forced expiratory volume (FEV1) decreased; carbon monoxide diffusion capacity (DLCO) decreased; vital capacity abnormal)

Patients enrolled to this study may have some degree of impaired pulmonary function as measured by pulmonary function tests (PFTs), including Forced Expiratory Volume in 1 second (FEV_1), Forced Vital Capacity (FVC), and Diffusing Capacity for Carbon Monoxide (DLCO). The CTCAE Version 4 grading criteria for PFTs assume that all patients have normal baseline pulmonary function. This assumption is not appropriate for this protocol, which is enrolling patients with abnormal baseline function. In order to monitor changes in lung function from baseline, a protocol-specific toxicity classification for PFTs has been developed for use with this study. PFTs will be coded for all patients in both treatment groups using this scale. See RTOG Pulmonary Function Test Toxicity Scale (Section 11.3) for more information.

Other Grade 3 or Higher Adverse Events

All other adverse events Grade 3 or higher, or requiring suspension of therapy, will be reported.

6.4 Compliance Criteria

6.4.1 Dosimetry Compliance

The JoLT-Ca quality assurance team will evaluate dosimetry plans. RT treatment plans not meeting the “per protocol” criteria or scored as “variation acceptable” will be classified as “deviation unacceptable.” Normal tissue dose constraints are listed in section 6.0. **NOTE: For the spinal cord, these are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation.** For the non-spinal cord tissues, acceptable deviation allows a maximum point dose no more than 105% of the prescription dose (56.7 Gy or 18.9 Gy per fraction) while fully respecting the defined volume constraint (for serial tissues) OR exceeding the parallel tissue critical volume dose maximum by no more than 5%. Unacceptable deviation exceeds the volume constraint for serial tissues, exceeds the maximum point dose for serial tissues by more than 105% of the prescription dose, or exceeds the parallel tissue critical volume dose maximum by more than 5%.

6.4.2 Contouring Compliance

Accurate and appropriate contouring is essential for the generation of dose volume statistics. As such, we require that the tumor targets, lungs, esophagus, bronchial tree, spinal cord, heart (pericardium), and trachea be contoured in all patients. In addition, any structure listed with a constraint in Critical Structures and residing within 10 cm in any direction from the PTV must be contoured. Appropriateness of contouring will be scored by the study PIs as either no deviation, minor deviation, or major deviation.

6.5 SAbR Quality Assurance Documentation

6.5.1 Quality Assurance Requirements

Surgical quality assurance will be performed by the surgical study chair or designee and recorded in a study specific surgical QA form. SAbR quality assurance will be conducted by JoLT-Ca Radiation QA headquarters at UTSW in Dallas.

6.5.2 Surgery Quality Assurance

All operative and pathology reports will be reviewed by the surgical study chair or designee for success of the resection. Problems or concerns about investigator performance will be communicated directly to the investigator by the study chair.

6.5.3 SAbR Quality Assurance

SAbR quality assurance documentation (recorded in study specific QA form) and DICOM RT datasets will be submitted to JoLT-Ca Radiation QA headquarters on all patients for review. Some identified sites based on credentialing category will need to submit this information on the first patient treated at that site prior to start of SAbR (the site credentialing letter will clarify this requirement). The following materials will be submitted for each patient:

- Planning CT images (DICOM)
- Structure contours (DICOM RT Structure Set) for critical normal structures, all GTV, ITV, and PTV contours. For critical normal structures identification, use the bold font names in section 6.2.
- Treatment plan (DICOM RT Plan) for initial and boost beam sets
- 3-D CALCULATED dose distributions (DICOM RT Dose) for initial and boost sets of concurrently treated beams
- Color isodose images in axial, sagittal, and coronal planes (JPEG or PNG screen captures)
- DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan (DV)
- Digital Data Submission Information Form (DDSI)

The required digital datasets must be submitted as DICOM RT objects. Prior to data submission, all DICOM objects have to be de-identified with a provided DICOM de-identification tool.

6.5.4 Rapid Review of Treatment Plan for First Patient

Rapid review of the first patient's treatment plan prior to treatment is required for each institution. This rapid review is waived if the institution already performed such first case review on one of the following RTOG trials: 0236, 0813, 0618, 0915, and 1021.

The rapid review allows the study team to determine the institution's ability to generate a "per protocol" treatment plan. Each institution must digitally submit the planning CT dataset with the proposed treatment plan prior to the start of treatment for the first patient registered by the institution. The plan will be reviewed centrally by the study co-chair or designee, and suggestions regarding protocol compliance will be forwarded to the participating institution.

6.5.5 Treatment Plan Review for Subsequent Patients

Only the first patient's treatment plan at each site will be reviewed prior to treatment. For all subsequent patients, the study co-chair or designee will perform retrospective treatment plan review after complete data for the first 50 cases enrolled have been received at JoLT-Ca radiotherapy QA headquarters. Subsequent reviews will be performed for every 50 patients enrolled and treated with SAbR thereafter.

6.5.6 Required Materials for Subsequent Patients

Within four weeks after completion of SAbR, submit the required materials identified in Section 6.6.3 for all patients.

The required datasets must be submitted digitally as DICOM RT objects.

6.5.7 Final Dosimetry Data Submission for All Patients

Within four weeks after completion of SAbR, submit hard copies of the following for all patients:

- Radiotherapy Summary Form

6.6 QA Submission Instructions

All CT planning and treatment information (e.g., planning CT files, dose files, plan files, and structure files) must be submitted digitally in DICOM RT format. Plan report including isodose distributions, DVHs and dose statistics in PDF format shall also be submitted along with digital DICOM RT datasets.

A Secure FTP (SFTP) account with username and password can be obtained by contacting UT Southwestern Medical Center-Department of Radiation Oncology, Yulong.yan@utsouthwestern.edu.

Sites must notify via e-mail when digital data are submitted. The e-mail must include the study and patient identification numbers and a description of the datasets being submitted (e.g.QA, SAbR treatment plan, etc.).

7.0 SYSTEMIC THERAPY

Arm 1 patients found at surgery to have pathological Stages Ib, IIa, IIb and IIIa may be offered adjuvant systemic therapy at the discretion of the treating physician.

Arm 2 patients with clinical Stage Ib after protocol therapy is completed may be offered systemic therapy at the discretion of the treating physician.

Any non-protocol therapy administered to the patient must be documented in the patient's hospital/clinic chart.

8.0 EARLY DISCONTINUATION OF PROTOCOL THERAPY

Protocol therapy may be discontinued early at the discretion of the investigator for the following reasons:

- Excessive or unacceptable toxicity
- Patient refusal or withdrawal of consent for treatment
- Disease relapse/progression during therapy

9.0 FOLLOW-UP

9.1 Follow-up of Patients Who Refuse Pre-Randomized Treatment Arm

Registered patients who refuse to consent to the treatment arm they have been pre-randomized to will be offered consent to be followed as required by the Study Calendar. Patients who refuse both the pre-randomization assignment and observation after standard of care treatment will be off study.

9.2 Follow-up of Patients with Disease Relapse/Progression

Patients with primary tumor associated, regional nodal, or distant disease relapse/progression or development of a second primary during or after protocol therapy will be followed for survival status only as required by the Study Calendar. NOTE: Patients may be treated for relapsing disease at the physician's discretion. NOTE: If resection is attempted after disease relapse/progression, submit operative and pathology reports and 4-week post-surgery adverse event data.

9.3 Follow-up of Patients Who Discontinue Treatment Early for Reasons Other Than Disease Relapse/Progression

Patients who discontinue protocol therapy for reasons other than disease relapse/progression will be followed as required by the Study Calendar. In cases where patients refuse further follow-up reasonable queries should be made as appropriate as to living/dead status and date of death (if applicable).

9.4 Follow-up of Arm 1 Patients with Benign Disease on Final Pathology

Arm 1 patients with benign disease on final pathology will be followed for adverse events, survival as required by the Study Calendar. No post-operative scans or blood specimen submission will be required.

9.5 Study Calendar[12]

Tests and Observations	Within 60 days prior to randomization. (except where noted)	After reg. and before SAbR or surgery	Both arms (From date of surgery/end of SAbR) [±2 weeks window on each time point][5]									Every 6 mo. thereafter until 60 mo.[6]	At time of disease relapse / PD[13]
			4 weeks	3 mo.[11]	6 mo.	9 mo.[11]	12 mo.	15 mo.[11]	18 mo.	21 mo.[11]	24 mo.		
History & Physical, ECOG/Zubrod PS	X		X	X	X	X	X	X	X	X	X	X[7]	X
Pregnancy test (urine or serum)	X[1]												
Tumor biopsy (required) and LN biopsy (if needed)	X[9]												X[3b]
Pulmonary Function Tests	X[8]			X	X		X				X		
PET/CT scan chest/upper abdomen	X[10]				X[3a]		X[3a]				X[3a]		X[3a]
CT scan chest/upper abdomen				X		X		X	X	X		X	X
Adverse event assessment	X	X	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]		X[4]
Charlson Comorbidity Index		X											
LCSS[14]		X	X	X	X		X				X	X	
QA submission to JoLT-CA Radiotherapy QA Headquarters		X[2]	X										

1 For patients of childbearing potential.

2 Submission to JoLT-CA Radiotherapy Headquarters of the first radiation (randomized to RT and accepted the randomization) patient's treatment plan prior to treatment for each site unless waived (per 6.6.4). Otherwise the treatment plan needs to be submitted after RT is completed.

3a During post-treatment follow-up, CT scan may be substituted for PET/CT if PET/CT will not be reimbursed by the patient's insurance. The reason for each deviation from the protocol must be documented in patient records.

3b In any instance a CT alone is suspicious for relapse/progression; biopsy of relapse/progression sites is highly recommended but not required. However, if biopsy is not performed, PET/CT must be performed to confirm disease. Submission of biopsy pathology report (if applicable) and scan reports is required. After disease relapse/progression or development of a secondary primary, patients will be followed for survival status as required by the Study Calendar. Adverse events will be followed

4 Adverse event assessments are required for all patients during the first 24 months after completion of protocol therapy, unless disease relapse/progression happens prior to the 24 month time point.

5 Arm 1 patients (surgery) with benign disease on final pathology will be followed for survival status.

6 It is highly recommended that patient should be followed every 6 months after month 24 (at month 30, 36, 42, 48, 54, 60) for 5 years. A minimum of annual follow up is required. Any additional studies may be performed at the treating physician's discretion as needed.

7 Patients who refuse to accept randomization but consent to be observed need to be followed as per point 6 above.. Any additional studies may be performed at the treating physician's discretion.

8 Baseline PFTs are required within 180 days prior to randomization. PFTs must include routine spirometry and DLCO. Arterial blood gases are not required but may be used as minor criteria for study enrollment. See Eligibility Criteria.

9 Tumor biopsy is required within 180 days prior to randomization.

10 PET/CT scan is required within 180 days prior to randomization.

11 It is highly recommended to follow up with patient every three months for the first 24 months. Patient will be followed at least every 6 months in any circumstance during the first two years.

12 If a given patient's health care payer refuses payment for any study evaluation, that evaluation may be omitted. However, documentation of this refusal must be available.

13 See section 9.2.

14 Lung Cancer Symptom Scale

9.6 Quality of Life Measures

Lung Cancer Symptom Scale (LCSS) - The LCSS (see Appendix G) is designed as a site-specific measure of quality of life (QL), particularly for use in clinical trials. It evaluates six major symptoms associated with lung malignancies and their effect on overall symptomatic distress, functional activities, and global QL. The philosophy behind the development of the LCSS is to provide a practical QL measure that reduces patient and staff burden in serial measurement of QL during the course of the trial. It captures in detail those dimensions most likely to be influenced by therapeutic interventions and evaluates other dimensions globally. Detailed information on this extensively used assessment is available at http://www.lcss-ql.com.

10.0 EVALUATION OF OUTCOMES

Type of Recurrence	Modality	Description (after treatment effects have subsided)
Failures Associated with the Primary Tumor		
Primary tumor failure (PTF)	SAbR	Appearance of residual tumor located within the extent of the primary targeted tumor.
Marginal failure (MF) (includes suture/staple line recurrence)	SR/SAbR	SR: Appearance of tumor $\leq$ 2 cm in any direction of the staple-line including the structures immediately adjacent to prior tumor site (chest wall/ mediastinum/ diaphragm/ spine). SAbR: Appearance of tumor $\leq$ 2 cm in any direction of the primary tumor including structures immediately adjacent to primary tumor (lung/ chest wall, mediastinum/ diaphragm/ spine).
Involved Lobe failure (ILF) (Including intrapulmonary LNs station 12-14 indistinguishable from satellite nodules)	SR/SAbR	SR: Appearance of tumor > 2 cm in any direction of the staple-line but within the residual named lobe containing the original primary tumor. SAbR: Appearance of tumor > 2 cm in any direction of the primary tumor within the named lobe containing the original primary tumor.
Port site/wound failure (PWF)	SR	Appearance of tumor at a port or incision site after VATS or open resection.
Failures within Regional Lymph Nodes		
Ipsilateral hilar nodal failure (HNF)	SR/ SAbR	Appearance of tumor in ipsilateral hilar or peribronchial (station 10-11) lymph nodes
Ipsilateral mediastinal nodal failure (MNF)	SR/ SAbR	Appearance of tumor in ipsilateral mediastinal (stations 2-6, 8, 9) and/or subcarinal (station 7) lymph nodes.
Distant nodal failure (DNF)	SR/ SAbR	Appearance of tumor in supraclavicular or scalene (station 1) or contralateral mediastinum (station 2.4), or contralateral hilum (station 10-11) lymph nodes.
Distant Recurrence		
Non-primary lobe failure (NLF)	SR/ SAbR	Appearance of tumor within another ipsilateral (non-primary) lobe.
Distant metastatic failure (DMF)	SR/ SAbR	Appearance of tumor deposits characteristic of NSCLC metastasis (intrathoracic areas not listed under primary tumor failures including the thoracic cavity/chest wall, mediastinal structures/diaphragm, malignant pleural effusion/pericarial effusion), contralateral lung and/or other distant organs/sites.

All patients will be followed for 5 years post treatment as specified in the study calendar (section 9.5). Adverse events including surgical morbidity and mortality and late radiation effects also will be monitored per study calendar and section 11.

10.1 Response to SAbR

Response to SAbR will be assessed and reported according to RECIST Version 1.1 criteria.

Evaluation of Target Lesions (Primary Tumor)

- **Complete Response (CR)**: Disappearance of the target lesion.
- **Partial Response (PR)**: At least a 30% decrease in the diameter of target lesions, taking as reference the baseline diameter.
- **Progressive Disease (PD)**: At least a 20% increase in the diameter of the target lesion, taking as reference the smallest diameter on study (this includes the baseline diameter if that is the smallest on study). In addition to the relative increase of 20%, the diameter must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD)**: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest diameter while on study.

10.2 Relapse/Progression Definitions

All patients will be assessed for disease relapse/progression according to the categories of the table in 10.0. The patterns of failure (local, regional, and distant) will be recorded to determine if there are differences in the pattern of relapse/progression between arms.

Biopsy or PET/CT is required to confirm disease relapse/progression (i.e., if CT scan alone is suspicious for relapse/progression, then PET/CT is required to confirm disease status). PET uptake defining recurrence should be prominent and with a SUV within tumor value similar to original staging PET. Equivocal interpretation should encourage biopsy. Biopsy confirmation of relapse is highly recommended but not absolutely required. When biopsy is feasible, the following methods are recommended: fine-needle or core aspiration biopsy, EBUS, EUS, VATS or open biopsy.

CT imaging at three months will be considered the new baseline to account for inflammatory changes and fibrosis after SAbR or SR. The table above describes the different areas defined as local, regional, and distant relapse/progression after treatment effects have subsided.

Particularly for the SAbR treatment, progression may be difficult to ascertain in comparison to scar tissue or other treatment related changes. Recurrence may be suspected based on imaging, but not definitely confirmed. If such changes are present, and follow-up confirms a recurrence, the recurrence should be post-dated to the time when the recurrence was first suspected.

11.0 ADVERSE EVENTS

11.4 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who

will enroll in future studies. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline or is stable in the opinion of the investigator;
- there is a satisfactory explanation other than the study therapy for the changes observed; or
- death.

11.4.1 Definition

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Acute Adverse Events

Adverse events occurring in the time period from the signing of the informed consent, through *4 weeks* post treatment will be considered acute adverse events. All events that take place during this time duration, no matter the category or relatedness, must be recorded.

Late Adverse Events (*as applicable*)

Adverse events occurring in the time period from the end of acute monitoring, to *24* months (2 years) post treatment, will be defined as late adverse events. Visits used for adverse event evaluation include Radiation Oncology and Surgery. Specific events to be evaluated are listed below.

Surgery

Atelectasis, lung infection, pneumonitis, dyspnea, adult respiratory distress syndrome, pleural infection, thromboembolic event, myocardial infarction, ventricular arrhythmia, arterial injury, venous injury, wound infection, bronchopleural fistula, chronic pain (beyond peri-operative expectations), postoperative hemorrhage, sepsis, recurrent laryngeal nerve palsy, intraoperative respiratory injury, postoperative thoracic procedure complication, changes in pulmonary function tests (e.g., forced expiratory volume (FEV1) decreased; carbon monoxide diffusion capacity (DLCO) decreased; forced vital capacity abnormalities.

Stereotactic Ablative Radiotherapy

Pneumonitis, atelectasis, bronchial obstruction, bronchial stricture, bronchopleural fistula, chest wall pain, fracture, changes in pulmonary function tests (e.g., forced expiratory volume (FEV1) decreased; carbon monoxide diffusion capacity (DLCO) decreased; vital capacity abnormal), pulmonary fibrosis, burn, dermatitis radiation, alopecia, cough (may be productive), dyspnea, fever, fatigue, pericarditis, pericardial effusion, chest pain – cardiac, palpitations, heart failure, myocardial infarction, paresthesias, esophagitis, dysphagia, aortic or arterial injury, hemoptysis, pain of skin.

RTOG Pulmonary Function Test Toxicity Scale

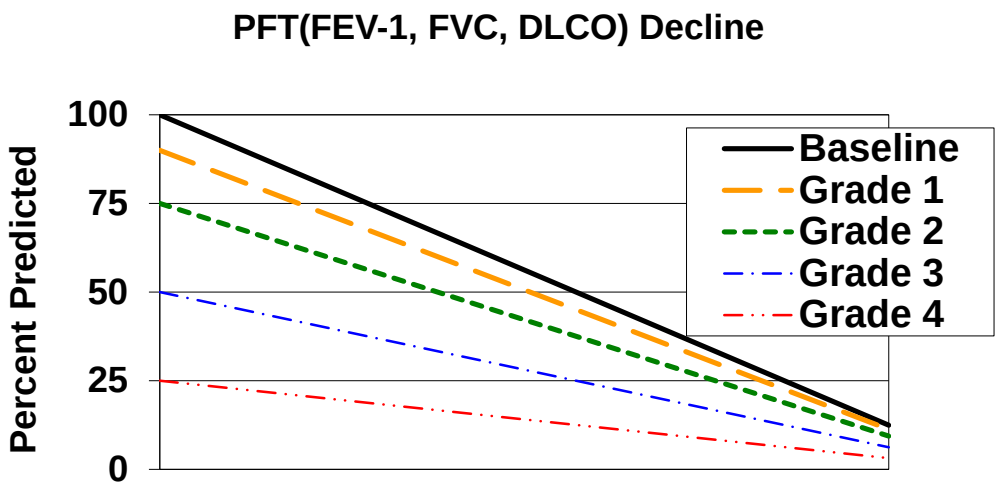
Changes in pulmonary function tests (FEV-1, FVC, DLCO, etc) for all patients will be graded using the RTOG Pulmonary Function Test Toxicity Scale. The RTOG Pulmonary Function Test Toxicity Scale is preferred for this protocol because it accounts for baseline abnormalities in pulmonary function which will be common based on the protocol's eligibility criteria.

Changes that occur after therapy will be referenced to baseline for a given patient, which will be abnormal for most patients. The RTOG scale defines a proportional decline from the baseline. Grade 1 toxicity will be a decline from baseline to a level 0.90 times the baseline, grade 2 will be a decline to a level 0.75 of baseline, grade 3 will be a decline to a level 0.5 of baseline, grade 4 will be a decline to a level 0.25 of baseline, and grade 5 will be death. This scheme is depicted in the table below and graphically represented in the figure below. Both arms of this trial will utilize this alternate pulmonary function toxicity scale rather than the CTCAE for grading and reporting changes in PFTs.

As an example, a patient who enters the study with a percent predicted DLCO of 55% who experiences a post treatment decline to a percent predicted DLCO of 40% would have a grade 4 event in the original CTCAE version 4 criteria; however, under this modified PFT toxicity classification for patients with abnormal baseline, his decline would constitute a decrease to 0.72 of the baseline value which is between 0.75 and 0.5 or a grade 2 event.

RTOG Pulmonary Function Test Toxicity Scale					
	Grade				
Adverse Event	1	2	3	4	5
FEV-1 Decline	0.90-0.75 times the patient's baseline value	<0.75-0.50 times the patient's baseline value	<0.50-0.25 times the patient's baseline value	<0.25 times the patient's baseline value	Death
Forced Vital Capacity Decline	0.90-0.75 times the patient's baseline value	<0.75-0.50 times the patient's baseline value	<0.50-0.25 times the patient's baseline value	<0.25 times the patient's baseline value	Death
DLCO Decline	0.90-0.75 times the patient's baseline	<0.75-0.50 times the patient's baseline	<0.50-0.25 times the patient's baseline	<0.25 times the patient's baseline value	Death

	value	value	value		



Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization[1,2] or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the

research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring ≥24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

[2] NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The phrase “unanticipated problems involving risks to subjects or others” is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

AND

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

11.4.2 Reporting

All SAE/UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs/UPIRSOs occurring during the protocol-specified monitoring period should be submitted to the SCCC DSMC within 5 business days of the PI or delegated study team members awareness of the event(s). In addition, for

participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events.

The UTSW study team is responsible for submitting SAEs/UPIRSOs to the SCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE/UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if further action is required. *(See Appendix III of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB is not required).*

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Comprehensive Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all SAEs/UPIRSOs upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

The following instructions section may be modified as needed to ensure clear guidance for institutions participating in the trial who will not report directly to the UTSW Institutional Review Board. If needed, this reporting may be facilitated by the UTSW study team for example.

SAE reports much be submitted witin 2 working days. PDFs of the report and source documents can be submitted to the UTSW's primary coordinator via email.
Written reports to: UTSW Radiation Oncology Coordinator Email: sarah.hardee@utsouthwestern.edu Fax: 214-645-7623 or deliver via PDF to email

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP/IRB

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP/IRB policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

For purposes of this policy, UPIRSOs include unanticipated adverse device effects

(UADEs) and death or serious injury related to a humanitarian use device (HUD).

UPIRSOs must be promptly reported to the UTSW IRB within 5 working days of PI awareness.

For research relying on a non-UT Southwestern IRB (external, central, or single IRB):

Investigators relying on an external IRB who are conducting research on behalf of UT Southwestern or its affiliates are responsible for submitting **LOCAL** UPIRSOs to the UT Southwestern IRB within 5 working days of PI awareness. Investigators must report to their relying IRB according to the relying IRB's policy. In addition, the external IRB's responses or determinations on these local events must be submitted to the UT Southwestern IRB within 10 working days of receipt.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/research-administration/irb/assets/policies-combined.pdf.

11.4.3 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *may NOT be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur *to the end of the acute adverse events reporting period as defined in section 11.4.1*). Any event that occurs more than 30 days after the last dose of treatment *during the late adverse event period as defined in section* 11.4.1 and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported as indicated in the sections below.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the treatment. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol (if applicable);
- the drug package insert (if applicable);
- the current Investigator's Brochure (if applicable)
- the Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities section of this protocol

12.0 STATISTICAL CONSIDERATIONS

12.1 Sample Size Determination

The sample size calculation is based on the primary endpoint, overall survival, and the assumption that patients are randomized until the end of accrual. The sample size is calculated with the 2-sided significance level of 0.05 and 80% statistical power using a 2-sample log rank test. We assume that the overall survival function follows an exponential distribution for each arm. Accrual to the study is assumed to be uniformly distributed. The null hypothesis is that there are no difference in overall survival rates between sublobar resection (SR) and Stereotactic Ablative Radiotherapy (SAbR) arms. We hypothesize that the patients randomly assigned to the SR arm and SAbR arm have a 3-year survival rate of 70% and 85%, respectively, which is translated to the hazard ratio of 0.456. One interim analysis for early stopping for efficacy or futility and two analyses for reporting purposes after accrual are planned. For the initial post accrual analysis which will report 3-year results, patients are assumed accrued over 3 years with minimum follow-up of 2 years from treatment of the last patient enrolled. The efficacy testing is based on the Lan-DeMets spending function [21], which resembles the O'Brien-Fleming boundary. For this initial analysis, the total sample size of 266 patients (109 in the SR arm,109 in the SAbR arm, and 48 patients who reject to consent to accept randomization assignment but consent to be observed after standard care of therapy) will have more than 80% statistical power at a 2-sided significance level of 0.05. Sample size was estimated using the sample size software PASS 13 [22]. Anticipating that 20% of patients will refuse treatment assignment, a further 54 patients will be enrolled to bring the final targeted accrual of the study to 272 patients. In addition to this initial analysis, a final analysis reporting 5-year results is also planned after additional follow-up (3 years for accrual and a minimum follow-up of 4 years from treatment of the last patient enrolled). With the additional follow-up, the statistical power of the second analysis improves to more than 90% under similar assumptions including the 266 patient target enrollment.

12.2 Selection, Conduct, and Analysis Plans

All eligible patients who are randomized to the study will be included in the comparison of treatment arms, regardless of treatment compliance.

A pre-randomization strategy will be used to avoid problems with patient lack of equipoise. Sites will screen for and identify patients eligible for the trial. These patients may be approached about the trial, given information about its rationale and conduct, and provided educational materials (e.g., the study's recruitment video, https://www.joltca.org/). As appropriate, these patients will be randomized by the central research office/statistical center to either the standard arm 1 (sublobar resection) or the experimental arm 2 (SAbR). The specific patient randomized assignment will be conveyed to the patient along with an opportunity to consent for the trial by accepting the randomization. If accepted, the patient will sign consent and be treated according to the assignment and followed. If rejected, the patient will be offered an opportunity to consent to be followed after standard of care treatment for progression free and overall survival on trial. If the patient rejects both opportunities to be consented for the trial, they will not be part of any protocol activities or followed on protocol. As such, despite the pre-randomization prior to consent, no protocol activity will be conducted without first obtaining informed consent.

It is assumed that 80% of consented patients will accept the pre-randomization and thereby meet accrual as anticipated. The central research office will verify that this percentage is being met during the conduct of the trial. If the actual acceptance rate is

significantly lower than 80%, the study committee will be notified for reactions which might include amending the protocol enrollment expectations, altering the methods of interacting with patients, or other strategies to ensure appropriate accrual. It is assumed that among the 20% rejecting the pre-randomization assignment, approximately 10% will also reject the request to be followed with standard of care treatment. Again, if this expectation not realized, the study committee will be notified for reaction.

The primary analysis will be carried out on an intent-to-treat basis. An intent-to-treat analysis may distort the treatment effect due to consent bias and selection bias. To deal with this problem, we will use the compiler average causal effect (CACE) analysis via principal stratification, which provides unbiased estimates of the treatment effect for patients who comply with the protocol (VanderWeele T, 2011).

12.3 Overall Survival

Overall survival time will be estimated using the Kaplan-Meier approach. The log-rank test will be used to test for a statistically significant difference in survival distributions. The null and alternative hypotheses are H_0: $S_1(t) = S_2(t)$ vs. H_A: $S_1(t) \leq S_2(t)$, where $S_1(t)$ and $S_2(t)$ are the distributions of overall survival times for patients in SR and SAbR arms. The Cox proportional hazard regression model will be used to determine hazard ratios and 95% confidence intervals for the treatment difference in overall survival. Unadjusted ratios and ratios adjusted for covariates of interest will be computed.

12.4 Progression Free Survival and Patterns of Failure

Progression free survival will be estimated using the Kaplan-Meier approach. The log-rank test will be used to test for a statistically significant difference in progression free survival between SR and SAbR arms. The null and alternative hypotheses are H_0: $S_1(t) = S_2(t)$ vs. H_A: $S_1(t) \leq S_2(t)$, where $S_i(t)$ is the distribution of survival times for patients in arm *i*, where arms 1 and 2 are SR and SAbR arms. The Cox proportional hazard regression model will be used to determine hazard ratios and 95% confidence intervals for the treatment difference in progression free survival. Unadjusted ratios and ratios adjusted for covariates of interest will be computed.

Log-rank tests will be used to investigate if local or regional recurrence and distant recurrence are significantly different between the two arms. The Cox proportional hazard regression model will be used to determine hazard ratios and 95% confidence intervals for treatment differences in local and regional recurrence and distant recurrence.

12.5 Toxicity

Only adverse events assessed to be definitely, probably, or possibly related to protocol treatment will be considered using the CTCAE. The rates of all Grade 3-5 adverse events, and death during or within 30 days of discontinuation of protocol treatment will be tested for equality using a two-sided chi-square test or Fisher's exact test with a 0.05 significance level.

12.6 Interim Reports to Monitor the Study Progress

Interim reports with descriptive statistics will be prepared annually until the initial paper reporting the treatment results has been accepted for publication. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase; data quality; compliance rate of treatment delivery with the distributions of important prognostic baseline variables; and the frequencies and severity of adverse events. The interim reports will not contain results from the treatment comparisons with respect to the primary or secondary endpoints. These reports will be distributed in writing (paper and/or electronically) to both the SCC DSMC and the trial's external DSMC.

12.7 Interim Analysis of Study Endpoints

There will be one interim analyses of the primary study endpoint (overall survival). The interim analysis will be conducted when half of all patients are accrued. If the p-value is smaller than 0.0077 at the interim analysis, then study discontinuation will be recommended to the Data and Safety Monitoring Committee (DSMC). The significance level was calculated to ensure an overall significance level of 0.05 (type I error). In addition, a conditional power analysis will be conducted at 50% accrual [23]. If the conditional power indicates less than 15% power to observe the alternative hypothesis, then a recommendation for study discontinuation will be made to the DSMC. The results of the interim analyses only will be reported, in a blinded fashion, to the DSMC.

A summary of serious adverse events, both anticipated and unanticipated, will be prepared at the time of the interim analysis and distributed to the DSMC, DSMB and the participating sites.

13.0 STUDY MANAGEMENT

13.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

13.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the each participating site's IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent

form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

13.3 Required Documentation (for multi-site studies)

Before the study can be initiated at any site, the following documentation must be provided to the UTSW Radiation Oncology CRO (JoLT-Ca Headquarters).

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list or Federal wide Assurance letter
- A copy of the IRB-approved consent form
- Signature/Delegation log
- Regulatory documents
- Executed clinical research contract

13.4 Registration Procedures

Pre-randomization in the Stablemate's Trial: Recommended Step by Step Instructions

1. **Assessing Eligibility:** Patients will typically be evaluated first by the thoracic surgeon to determine eligibility on the JoLT-Ca Stablemate's Trial based on biopsy proven non-small cell lung cancer, staging with PET/CT and node sampling as indicated, confirmed high-risk operable candidate based on pulmonary function tests, echocardiogram, and/or or modified medical research council dyspnea scale ≥ 3 (full inclusion criteria available in protocol). We understand that a needle biopsy of the primary tumor is not always taken as an initial step in some surgical practices. But to do so is nonetheless reasonable, and the thoracic surgery leadership for the trial felt very strongly that a patient potentially randomized to radiation should have a biopsy. Therefore for feasibility, all patients will need a biopsy.

2. **Pre-Randomization:** The web-based portal for randomization will be accessed and the demographics and eligibility worksheets will be completed. Once this is completed, the patient will be randomized to either SR or SAbR. Prior to randomization, an eligibility checklist must be completed showing the patient meets all eligibility criteria. This eligibility checklist must be signed and dated by the enrolling physician. Once randomization has been completed the checklist must be uploaded to REDCap.

3. **Initial Discussions about the Trial:** It is left to the discretion of the enrolling physician as to the point along the care pathway that the trial is first introduced to the patient, either prior to or after pre-randomization. Acceptance may be better if the trial is first introduced prior to pre-randomization. However, in either case, enrolling physicians should not pressure or coerce patients into enrolling. Instead, enrolling physicians should serve as a resource providing information about the disease, work-up, treatment options, outcomes, and the trial. When meeting with the patient, the physician would convey in all cases that the standard of care in the high-risk operable setting is sublobar resection (SR) and describe its conduct and outcomes. As an educational resource to help educate patients and introduce the trial, the study committee has created a video for patients on their website (https://www.joltca.org/) that may be used as an aid for discussions at the investigator's discretion.

   Discussion may go as follows, "Sublobar resection is an appropriate treatment for your cancer, and we are prepared to provide you with this procedure. However, physicians across the country are investigating whether an alternative treatment known as stereotactic ablative radiotherapy (SAbR) may also be a viable alternate." The patient would be informed about the conduct and outcomes of SAbR. The physician would continue, "The trial to test SR vs SAbR is open at our center. You are eligible for the trial and have been pre-randomized to arm _x_." The physician should indicate that they support the trial and its design (i.e., they have equipoise), and feel it would be reasonable to accept the randomization assignment. However, the choice to accept or reject would rest with the patient.

4. **Patient Decisions and Consent:** Should the patient wish to proceed on the study per their pre-randomization arm, they will then provide informed consent. We anticipate that 80% will accept given the results from the NSABP B-06 trial utilizing a similar schema. If the patient's treatment arm is SR, they will undergo the procedure by their thoracic surgeon and continue with follow-up per the study calendar. If they are pre-randomized to SAbR, then referral will be made to a radiation oncologist who is experienced in the delivery of SAbR and will follow SAbR delivery as specified in the protocol. If the patient rejects their pre-randomization arm, they will then be asked whether they wish to provide informed consent to be followed after standard of care treatment on the study per protocol defined follow-up, as validation of the control arm. If they do, informed consent will be obtained, standard of care therapy will be provided, and the patient will continue with follow-up per the study calendar. However, if the patients rejects their pre-randomization arm and rejects the opportunity to be followed per the study protocol, they will continue with treatment and follow-up as determined by their treating physician, with emphasis that their participation in the trial is entirely voluntary and will have no consequences on their care should they wish to not participate. In these cases, which we believe will be rare, no patient specific information will have been conveyed to the central CRO despite the pre-randomization.

Once the consent process is complete, the acceptance form in REDCap should be answered fully and a copy if the consent and any consent notes (if applicable) must be uploaded to REDCap. Once the patient is consented please notify UTSW so a review of eligibility can be completed.

13.5 Data Management and Monitoring/Auditing

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements, as appropriate for the project

Treatment Arm will be automatically generated after the eligibility and demographic information is entered into REDCap, a web-based data capture program. All subjects consenting to participate in any aspect of the trial must be registered on REDCap before initiating protocol activities. All research data will be recorded and entered into Case Report Forms using REDCap. Online access will be provided to each study site by the UTSW Radiation Oncology CRO.

In order to facilitate remote source to case report form verification, the Simmons Comprehensive Cancer Center study team will require other institutions participating in this trial as sub-sites to enter data into the selected EDC system and upload selected de-identified source materials when instructed

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT and/or the CRO Multi-Center IIT Monitor. This review includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

For further information, refer to the UTSW SCCC IIT Management Manual.

The trial will have two data safety monitoring committees overseeing the conduct of the trial. First, the External Data Safety Monitoring Board (DSMB) is composed of notable/national early lung cancer and lung cancer statistical experts enlisted by JoLT-Ca. The second will be the UTSW Simmons Cancer Center (SCC) Data Safety Monitoring Committee (DSMC) who will serve as the DSMC of record.

The External DSMB will be made up of 3-4 people including a thoracic surgeon, radiation oncologist, and statistician from institutions not participating in the trial. Dr. Ahn, the statistician for the study, will also serve on the committee but without authority to vote. The External DSMB will be apprised of high grade adverse event on a monthly or every other month basis during accrual by the UTSW Radiation Oncology DOT and review the treatment-relation assignments made locally and by the UTSW DSMC. While they will not have authority to reverse decisions by the DSMC of record, they will provide input and ask for appropriate clarification in aiding in the final determinations. They will review the toxicity trends and make recommendations to the study committee as appropriate. They will review the QA reports regarding the conduct of both surgery and radiation therapy as per protocol guidelines again to make recommendations to the study committee for possible modifications or amendments. They will review issues related to treatment and follow-up including salvage therapies. They will review

accrual reports and acceptance of assignment (consenting) rates to insure the trial is performing as designed. They will be informed of results of audits to include in their assessments. Again, they will make recommendations to the study committee and DSMC of record about trial performance, including recommendations to close the study if not performing as designed.

Toxicity reviews will be performed annually remotely through REDCap and the regulatory information system at UTSW. These reviews will be documented written reports and distributed to all sites as needed.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

13.6 Adherence to the Protocol

Except for an emergency situation, in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

13.6.1 Exceptions (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:

- intentional on part of the investigator; or
- in the investigator's control; or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)

➢ **Reporting requirement**: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation.

13.6.2 Emergency Deviations: include any departure from IRB-approved research that is necessary to:

- avoid immediate apparent harm, or
- protect the life or physical well-being of subjects or others

➢ **Reporting requirement**: Emergency deviations must be promptly reported to the IRB within 5 working days of occurrence.

13.6.3 Major Deviations (also called **violations**): include any departure from IRB-approved research that:

- Harmed or placed subject(s) or others at risk of harm (i.e., did or has the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

➢ **Reporting requirement**: Major deviations must be promptly reported to the IRB within 5 working days of PI awareness.

13.6.4 Minor Deviations: include any departure from IRB-approved research that:

- Did not harm or place subject(s) or others at risk of harm (i.e., did not or did not have the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Did not affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

➢ **Reporting requirement**: Minor deviations should be tracked and summarized in the progress report at the next IRB continuing review.

13.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the study co-chairs. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

13.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

13.9 Obligations of Investigators

The subsite Principal Investigators are responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

14.0 APPENDICES

Appendix A. Staging Reference (AJCC Cancer Staging Manual, 7th Edition, 2010)

Primary tumor (T)	
Tx	Primary tumor cannot be assessed, or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (e.g., not in main bronchus)*
T1a	Tumor 2 cm or less in greatest dimension
T1b	Tumor more than 2 cm but 3 cm or less in greatest dimension
T2	Tumor more than 3 cm but 7 cm or less or tumor with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less): • Involves main bronchus, 2 cm or more distal to the carina • Invades visceral pleura (PL1 or PL2) • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor more than 3 cm but 5 cm or less in greatest dimension
T2b	Tumor more than 5 cm but 7 cm or less in greatest dimension
T3	Tumor more than 7 cm or one that directly invades any of the following: parietal pleura (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina* but without involvement of the carina); or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe
Nodal Involvement (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed

M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe, tumor with pleural nodules or malignant pleural (or pericardial) effusion**
M1b	Distant metastasis

* The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1

** Most pleural (and pericardial) effusions associated with lung cancer are due to tumor. In a few patients, however, multiple cytopathological examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is not bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.

Appendix B. Stage Grouping

Stage	TNM
IA	T1a N0 M0 T1b N0 M0
IB	T2a N0 M0
IIA	T2b N0 M0 T1a N1 M0 T1b N1 M0 T2a N1 M0
IIB	T2b N1 M0 T3 N0 M0
IIIA	T1a N2 M0 T1b N2 M0 T2a N2 M0 T2b N2 M0 T3 N1 M0 T3 N2 M0 T4 N0 M0 T4 N1 M0
IIIB	T1a N3 M0 T1b N3 M0 T2a N3 M0 T2b N3 M0 T3 N3 M0 T4 N2 M0 T4 N3 M0
IV	Any T Any N M1a Any T Any N M1b

Appendix C. ECOG/Zubrod Performance Status Scale

0 - Asymptomatic and fully active.

1 - Symptomatic; fully ambulatory; restricted in physical strenuous activity.

2 - Symptomatic; ambulatory; capable of self-care; more than 50% of waking hours are spent out of bed.

3 - Symptomatic; limited self-care; spends more than 50% of time in bed, but not bedridden.

4 - Completely disabled; no self-care; 100% bedridden.

Appendix D.

Radiotherapy Summary Form

Institution Name:

Patient Initials:

Radiation therapy start date	
Radiation therapy end date	
Elapsed Days	
RT Total Fraction Count	
RT Total Dose (Gy)	
Number of days radiotherapy interrupted due to toxicity	
Number of days radiotherapy interrupted due to other reasons	
Reason Treatment Ended	1. Treatment completed per protocol criteria 2. Disease progression, relapse during active treatment 3. Adverse event / side effects / complications 4. Death on study 5. Patient withdrawal / refusal after beginning protocol therapy 6. Patient withdrawal / refusal prior to beginning protocol therapy 7. Other

Person Completing Form Date

Appendix E. Patient Education Video Script

Stablemates Trial
Ensayo de Stablemates
Surgery vs. SABR
Cirugía vs. SABR
VOICEOVER

A clinical trial is a study conducted to evaluate new medical treatments. Each study is designed to find better ways to help patients.
Un ensayo clínico es un estudio conducido para evaluar tratamientos médicos nuevos. Cada estudio está diseñado para encontrar mejor maneras para ayudar a los pacientes.
The Stablemates trial is now being offered to patients with early stage lung cancer to help evaluate whether a newer type of radiation treatment, called SABR, is as effective as surgery for treating this type of cancer.
El ensayo de Stablemates se ofrece ahora para pacientes con cáncer de pulmón en etapa temprana, para ayudar a evaluar si una forma más nueva de tratamiento de radiación llamado SABR es tan efectiva como la cirugía para tratar este tipo de cáncer.
The standard therapy for early-stage lung cancer is surgery.
La terapia general para cáncer de pulmón en etapa temprana es cirugía.
The preferred surgical procedure is called a lobectomy because a defined portion of the lung – called a “lobe” – is removed. Patients who are considered to be at high-risk for such an operation, but can still tolerate anesthesia and a more limited operation, may have a sublobar resection, that is, removal of less than a lobe. If you are watching this video, your doctor has determined that you are at higher risk for complications from a full lobectomy. Usually you would be offered the less invasive sublobar surgery as standard of care treatment.
El procedimiento quirúrgico preferido se llama lobectomía porque una porción definida del pulmón –llamado un “lóbulo” – es removido. Los pacientes que son considerados de alto riesgo para este tipo de operación pero que aún pueden tolerar anestesia y una operación más limitada, pueden tener una resección sublobar, lo cual es la eliminación de menos de un lóbulo. Si usted este viendo este video, su doctor ha determinado que usted está en mayor riesgo de complicaciones de una lobectomía completa. Usualmente se le ofrecería la cirugía sublobar menos invasiva como práctica de atención estándar.

[Fade in text on blue background] SABR
Radioterapia Estereotáctica Ablativa

VOICEOVER

As an alternative, in this study you could receive Stereotactic Ablative Radiotherapy, or SABR.
Como alternativa, en este estudio usted puede recibir Radioterapia Estereotáctica Ablativa, o SABR.

This new treatment uses highly focused radiation to destroy lung cancer while minimizing radiation exposure to surrounding normal tissue. Until now, SABR has been recommended exclusively for medically inoperable patients. The results of treating these patients with SABR have been much better than treatment with traditional radiation therapy, and may even offer as good an outcome as sublobar resection.
Este nuevo tratamiento utiliza un haz de radiación altamente enfocada para destruir cáncer de pulmón mientras minimiza la exposición de radiación a los tejidos normales que lo rodean. Hasta ahora, SABR (por sus siglas en inglés) se ha recomendado exclusivamente para pacientes medicamente inoperables. Los resultados de tratar a estos pacientes con SABR (por sus siglas en inglés) han sido mucho mejor que el tratamiento con radioterapia tradicional e incluso puede ofrecer resultados tan buenos como los de resección sublobar.

[Fade in text on blue background] Surgery vs. “SABR”

So now we want to know if there might be two options for early-stage lung cancer patients: Surgery and SABR. This study will help doctors understand the advantages and disadvantages of each therapy so that they can better advise patients about their treatment options. The study may also help physicians to identify which patients are more likely to benefit from one therapy compared to the other.
Ahora queremos saber si quizás puede haber dos opciones para pacientes con cáncer de pulmón en etapa temprana. Cirugía y SABR (por sus siglas en inglés). Este estudio ayudará a los médicos a entender las ventajas y desventajas de cada terapia para poder aconsejar mejor a los pacientes sobre sus opciones de tratamiento.

DR. FERNANDO

With sublobar resection the cancer is completely removed, as well as other areas that may contain cancer that we did not know about on preoperative testing. This may help reduce the chance of cancer recurrence and also may help guide future treatment such as chemotherapy. Remember, that with surgery the cancer is removed from the body; with other treatments the cancer is treated within the body.
Con la resección sublobar el cáncer es eliminado por completo, al igual que otras áreas que pueden contener cáncer del cual no sabíamos durante las pruebas preoperatorias. Esto puede ayudar a reducir el riesgo de recurrencia del cáncer, y también puede ayudar a guiar el futuro tratamiento como la quimioterapia. Recuerde que con la cirugía el cáncer es extraído del cuerpo; con otros tratamientos el cáncer es tratado dentro del cuerpo.

It’s important to remember that with surgery there is a recovery time, and also the risk of complications. Patients who are at high risk may have impaired lung function and may also have other medical problems that may impact their recovery. So why we think that surgery may be a good option, we have to think

about the time to recovery back to recovery and also that risk of complications that may exist.
Es importante recordar que con la cirugía hay un tiempo de recuperación, y también el riesgo de complicaciones. Los pacientes que son de alto riesgo pueden tener problemas de la función pulmonar y también pueden tener otros problemas médicos que pueden afectar su recuperación. Entonces, mientras pensamos que la cirugía puede ser una buena opción, tenemos que pensar en el tiempo de recuperación y también el riesgo de complicaciones que pueden existir.

DR. TIMMERMAN
We did a study a few years ago treating inoperable lung cancer patients with SABR, and we found that this treatment successfully controlled the targeted primary tumor in 98 percent of patients. This was very exciting, because they were given a very effective treatment that could be compared to surgery in terms of immediate tumor control and long-term survival. As a result of this study, the standard of care has completely changed for inoperable lung cancer patients.
Conducimos un estudio varios años atrás donde tratamos con SABR, a pacientes inoperables con cáncer de pulmón, y encontramos que este tratamiento controló con éxito el tumor primario dirigido en el 98 por ciento de pacientes. Esto fue muy emocionante porque se les proporciono un tratamiento muy efectivo que puede compararse a una cirugía en términos de control inmediato del tumor y la supervivencia a largo plazo. Como resultado de este estudio, la práctica de atención estándar ha cambiado por completo para pacientes inoperables con cáncer de pulmón.

So now we'd like to test this same treatment in patients who are eligible to have surgery, but who can't tolerate a full lobectomy. As a non-invasive, outpatient treatment, SABR may benefit patients by offering them a treatment that is easier to tolerate and that doesn't interfere greatly with their normal daily living activities.
Así que ahora nos gustaría probar este mismo tratamiento en los pacientes que son elegibles para obtener cirugía pero que no pueden tolerar una lobectomía completa. Como tratamiento no invasivo de consulta externa, SABR (por sus siglas en inglés) puede beneficiar a los pacientes ofreciéndoles un tratamiento que es más fácil de tolerar y que no interfiere grandemente con sus actividades del diario vivir.

[Text on blue background, fade in each bullet point to accompany voiceover]
Eligibility
* Biopsy-confirmed non-small cell lung cancer
* Tumor less than 4 centimeters
* No cancer in the regional lymph nodes, and no metastatic cancer lesions
* Performance status
* High risk for lobectomy
Elegibilidad
*Biopsia confirmada de cáncer de pulmón no microcítico
*Tumor menos de 4 centímetros

*No cáncer en los ganglios linfáticos regionales y sin lesiones cancerosas metastásicas
*Estado funcional
*De alto riesgo para lobectomía

TIMMERMAN VOICEOVER

To determine whether you are eligible to participate in the Stablemates clinical trial, your doctor will look at several criteria.
Para determinar si usted es elegible para participar en el ensayo clínico de Stablemates, su médico repasara varios criterios.

* First, you must have a diagnosis of non-small cell lung cancer confirmed by a biopsy.
*Primero, usted debe tener un diagnóstico de cáncer de pulmón no microcítico confirmado atreves de una biopsia.

* The tumor must be relatively small, less than 4 centimeters
*El tumor debe ser relativamente pequeño, menos de 4 centímetros.

* All lymph nodes in the chest cavity must be determined to be free of cancer, and there should be no spreading of the cancer to other sites.
*Todos los nódulos linfáticos de la cavidad pulmonar deben ser determinados libre de cáncer, y no debería haber ninguna difusión del cáncer a otros sitios.

* Doctors use a standardized scale to evaluate how well patients are coping with their activities of daily living. To participate in this trial you must be able to cope with daily self-care activities unassisted, such as using the bathroom and eating, even if you are too ill to go to work or engage in other activities outside the home.
*Los médicos utilizan una escala estandarizada para evaluar lo bien que van los pacientes con sus actividades diarias. Para participar en este ensayo deber ser capaz de hacer frente a las actividades de cuidado personal sin ayuda, como ir al baño y comer, aun si usted está demasiado enfermo para ir a trabajar o participar en otras actividades fuera del hogar.

* Finally, you have been determined to be at high risk for a lobectomy procedure. By now you will have had several tests to evaluate your heart and lung function. The outcome of these tests will determine your risk category.
*Finalmente se le ha determinado que esta en alto riesgo para un procedimiento de lobectomía. Hasta ahora usted habrá tenido varias pruebas para evaluar la función de su corazón y pulmón. El resultado de estas pruebas determinará su categoría de riesgo.

DR. TIMMERMAN

Every patient who meets the criteria for the clinical trial is prerandomized by computer assignment to either have surgery or SABR. All patients will be informed which treatment they've been assigned to before agreeing to participate in this

trial. At this point the patient can choose to accept the assignment or reject it - it is completely up to the patient. By accepting, they will receive the assigned treatment, either surgery or SABR, in the next few weeks. Even if the patient prefers not to accept the study assignment, they can still participate in the trial choosing a treatment along with their doctor. We deliberately designed the trial this way to give patients more control over the type of treatment they receive.
Cada paciente que cumple los criterios para el ensayo clínico es previamente seleccionado aleatoriamente por asignación de computadora para tener cirugía o SABR. Se les informara a todos los pacientes sobre cual tratamiento se les ha asignado antes de aceptar a ser partícipe de este ensayo. En este momento el paciente puede optar por aceptar la asignación o rechazarla, es completamente a discreción del paciente. Al aceptar, ellos recibirán el tratamiento asignado, ya sea cirugía o SABR. Durante las próximas semanas. Aun si el paciente decide no aceptar la asignación del estudio, todavía pueden participar en el ensayo y escoger un tratamiento junto con su médico. Nosotros deliberadamente diseñamos el ensayo de esta manera para darles a los pacientes más control sobre el tipo de tratamiento que reciban.

For SABR, patients first have a CT to verify the treatment location. The treatment itself is divided into three sessions, so patients will have three more visits to the radiation oncology clinic, usually for no more than 30 minutes each time, to complete the therapy. The treatment itself is completely painless. You don't feel it any more than you would feel a radio wave or a cell phone signal.
Para SABR, los pacientes primero deben de obtener una tomografía computarizada para verificar el sitio de tratamiento. El tratamiento en si está dividido en tres sesiones, por lo cual los pacientes tendrán tres visitas más a la clínica de oncología de radiación, por lo general no más de 30 minutos cada vez para completar la terapia. El tratamiento en si es completamente libre de dolor. Usted no siente más de lo que sentiría una onda de radio o una señal de teléfono celular.

DR. FERNANDO

For patients who agree to accept the standard treatment of surgery, a minimally invasive technique called a wedge resection or segmentectomy will be performed.
Para los pacientes que están de acuerdo en aceptar el tratamiento estándar de cirugía, se les hará una técnica invasiva llamada resección en cuña o segmentectomía.

We aim to confirm a margin of at least 1 cm around the tumor, so the chance of complete cancer removal is high. Usually one or two tubes are placed inside the chest, and when these are removed the patient can go home. Typically the patient will be at a reduced level of activity for about a month and then return back to normal.
Nuestro objetivo es confirmar un margen de por lo menos 1 cm alrededor del tumor, así que la posibilidad de eliminación completa del cáncer es alta. Por lo general, una o dos sondas se colocan dentro del pecho, y cuando se remueven el

paciente puede irse a casa. Normalmente el paciente estará a un nivel de actividad reducida por casi un mes y después regresara a la normalidad.

After a patient accepts their assignment and receives either surgery or SABR, they will have an initial follow-up visit at 4 weeks, they will return for follow-up testing every 3-6 months for the first two years, and every 6-12 months up to five years. We will ask those patients who do not accept their prerandomization assignment to allow us to monitor their progress as well. Tests will include a general physical, pulmonary function tests, CT scans and other tests that are routinely performed. There is no additional cost for any of these tests or for participating in the clinical trial.
Después de que un paciente acepta su asignación y recibe cirugía o SABR, ellos tendrán una cita de seguimiento inicial a las 4 semanas, regresarán para pruebas de seguimiento cada 3-6 meses durante los primeros dos años, y cada 6-12 meses hasta 5 años. Les pediremos a aquellos pacientes que no aceptaron su asignación aleatoriamente que también nos permitan monitorear su progreso. Las pruebas incluirán un físico general, pruebas de la función pulmonar, tomografías computarizadas y otras pruebas que se realizan rutinariamente. No hay costo adicional por ninguna de estas pruebas o por participar en el ensayo clínico.

Thank you for watching this presentation explaining the Stablemates Trial. If you have more questions, please talk to your doctor or clinical trial coordinator.
Gracias por ver esta presentación explicando el Ensayo Stablemates. Si usted tiene más preguntas, por favor hable con su médico o coordinador de ensayos clínicos.

Appendix F. Charlson Comorbidity Index

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Charlson Comorbidity Index (CCI)

Study ID	_____
Myocardial infarct	◯ Yes ◯ No
Congestive heart failure	◯ Yes ◯ No
Peripheral vascular disease	◯ Yes ◯ No
Cerebrovascular disease (except hemiplegia)	◯ Yes ◯ No
Dementia	◯ Yes ◯ No
Chronic pulmonary disease	◯ Yes ◯ No
Connective tissue disease	◯ Yes ◯ No
Ulcer disease	◯ Yes ◯ No
Mild liver disease	◯ Yes ◯ No
Diabetes (without complications)	◯ Yes ◯ No
Diabetes with end organ damage	◯ Yes ◯ No
Hemiplegia	◯ Yes ◯ No
Moderate to severe renal disease	◯ Yes ◯ No
2nd Solid tumor (nonmetastatic)	◯ Yes ◯ No
Leukemia	◯ Yes ◯ No
Lymphoma, MM...	◯ Yes ◯ No
Moderate or severe liver disease	◯ Yes ◯ No
2nd Metastatic solid tumor	◯ Yes ◯ No
AIDS	◯ Yes ◯ No
CCI total score	_____
Completed by	_____
Completion date	_____

09/22/2015 2:09pm www.projectredcap.org REDCap

CCI source

CCI source 2

Confidential

LCSS

Study ID _____

Date Completed _____

Please circle the one number below that describes how you would rate the symptoms of your lung cancer DURING THE PAST DAY.

	0 (As good as it could be)	1	2	3	4	5	6	7	8	9	10 (As bad as it could be)
1. How good is your appetite?	○	○	○	○	○	○	○	○	○	○	○
	0 (None)	1	2	3	4	5	6	7	8	9	10 (As much as it could be)
2. How much fatigue do you have?	○	○	○	○	○	○	○	○	○	○	○
3. How much coughing do you have?	○	○	○	○	○	○	○	○	○	○	○
4. How much shortness of breath do you have?	○	○	○	○	○	○	○	○	○	○	○
5. How much blood do you see in your sputum?	○	○	○	○	○	○	○	○	○	○	○
6. How much pain do you have?	○	○	○	○	○	○	○	○	○	○	○
	0 (I have none)	1	2	3	4	5	6	7	8	9	10 (As bad as they could be)
7. How bad are your symptoms from lung cancer?	○	○	○	○	○	○	○	○	○	○	○
	0 (Not at all)	1	2	3	4	5	6	7	8	9	10 (So much that I can do nothing for myself
8. How much has your illness affected your ability to carry out normal activities?	○	○	○	○	○	○	○	○	○	○	○
	0 (Very high)	1	2	3	4	5	6	7	8	9	10 (Very low)
9. How would you rate the quality of your life today?	○	○	○	○	○	○	○	○	○	○	○

Completed by ○ Participant ○ Staff

Entered by _____

Appendix H

jolt-ca | Joint Lung Cancer Trialist's Coalition

UTSouthwestern Medical Center

Research brings hope for cures.

Stablemates Clinical Trial

What is a clinical trial?

A clinical trial is a research study that is conducted in a medical setting, such as a clinic or hospital, that usually involves the testing of a new medication, treatment, or device. Patients are never placed in a clinical trial without their knowledge and permission. All qualified patients involved in clinical trials sign consent forms before the study begins.

What is the Stablemates trial?

The Stablemates trial compares two very effective standard therapies in their own right—BOTH of which have a history of being successfully used in the treatment of early stage lung cancer.

- Sublobar resection (surgery) has long been considered the standard treatment for early stage lung cancer. Surgical techniques have continued to advance in recent years, but there is still downtime after the procedure and a risk of complications.
- Stereotactic ablative radiotherapy (SAbR, also known as SBRT), is a newer radiation therapy technique that is completed in five painless, outpatient treatments of less than 30 minutes each. Recent clinical trials in SAbR have shown similar results as surgery in terms of cancer control, and it is now the standard of care given to inoperable patients.

If SAbR is so good, can it be used to treat a broader group—not just inoperable ones?

Determining which patients are best suited for either surgery or SAbR is one of the primary goals of the Stablemates trial.

How do I participate?

Stablemates is a little different than most other clinical trials. Usually, you agree first to participate and then are blindly randomized to a particular arm of the study. But we realize that it's important for cancer patients to have control over their treatment—so, you get to choose.

In Stablemates, patients are pre-randomized by a computer and then informed of their assignment before they choose to participate. If you don't like your assignment you are free to decline study participation and choose another therapy in consultation with your doctor.

With this approach, patients can weigh the pros and cons and make their own decisions.

You're in the driver's seat.

What else should I know?

- The Stablemates trial compares two different types of care that are normally provided for your disease. There are no unknown or experimental treatments being offered.
- There is no additional financial cost for participating in the study.
- We recommend that you discuss participating in Stablemates with your family and other potential caregivers before agreeing to participate in the study. Your doctor is also there to help answer questions so that you can make the best decision for YOU.
- The consent forms are long and can be difficult to understand. They include more detailed safety information and information about potential side effects. Ask your doctor or research nurse for assistance if you have questions while filling out these forms.
- You will be informed if any health risks are uncovered during the study that might influence your desire to participate in this clinical trial.
- You can change your mind about participating in the study at any time, including before or after you've received your treatment. Leaving the study will not affect the quality of your health care.
- A total of 272 people will be participating in the Stablemates clinical trial throughout the United States, Canada, and Australia.

Why is it called "Stablemates?"

The two therapies—surgery and SAbR—can be compared to two racehorses competing for the same prize (to cure patients with cancer), but cooperatively working together as long-time neighbors living in the same stable.

Lobectomy and SAbR have both demonstrated the ability to eradicate the primary lung cancer with a rate of around 90 percent in people with early stage, non-small cell lung cancer. However, patients suffering from lung cancer often have reduced cardiopulmonary function and other health challenges, which may put them at risk for undergoing an operation. For this reason, cancer researchers are interested in examining a noninvasive alternative to surgery for high-risk patients.

For more information, please visit the Stablemates trial web site at www.joltca.org.

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