STARS Revised Clinical Trial Protocol: Stereotactic Ablative Radiotherapy (SABR) in Stage I Non-small Cell Lung Cancer Patients Who Can Undergo Lobectomy.

Principal Investigator: Jack A. Roth, M.D.
Department of Thoracic and Cardiovascular Surgery
MD Anderson Cancer Center

Co-Principal Investigator: Joe Y. Chang, M.D., Ph.D.
Department of Radiation Oncology
MD Anderson Cancer Center

Co-Principal Investigator: Reza J. Mehran, M.D.
Department of Thoracic and Cardiovascular Surgery
MD Anderson Cancer Center

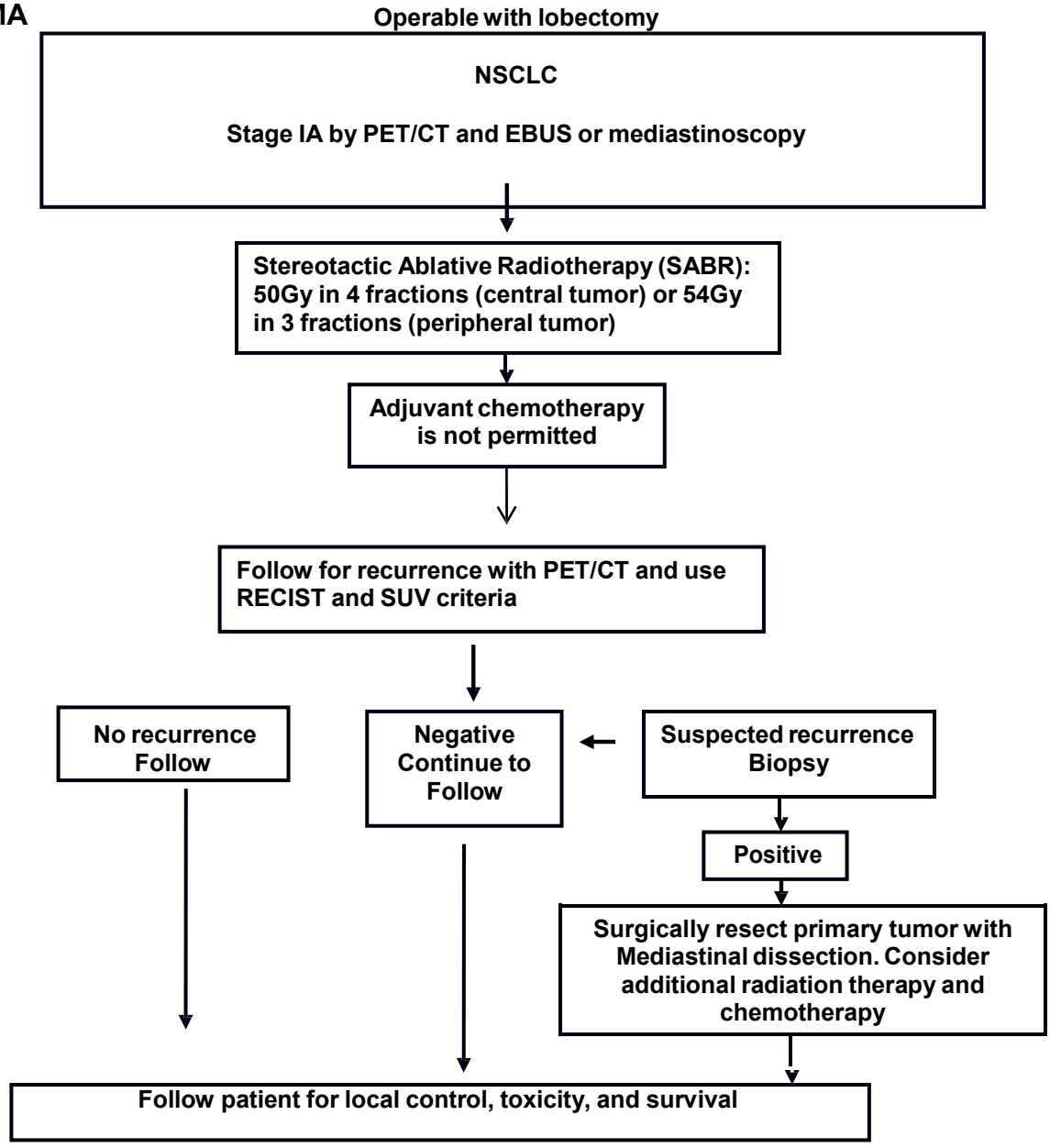
Co-Principal Investigator: Stephen McRae, M.D.
Department of Diagnostic Radiology
MD Anderson Cancer Center

Co-Principal Investigator: Peter Balter, Ph.D.
Department of Radiation Physics
MD Anderson Cancer Center

Co-Investigator: Lei Feng, MS
Principal Statistical Analyst
Department of Biostatistics
MD Anderson Cancer Center

Co-Investigator: Donald Berry, Ph.D.
Department of Biostatistics
MD Anderson Cancer Center

SCHEMA


Operable with lobectomy
NSCLC
Stage IA by PET/CT and EBUS or mediastinoscopy
Stereotactic Ablative Radiotherapy (SABR): 50Gy in 4 fractions (central tumor) or 54Gy in 3 fractions (peripheral tumor)
Adjuvant chemotherapy is not permitted
Follow for recurrence with PET/CT and use RECIST and SUV criteria
No recurrence Follow
Negative Continue to Follow
Suspected recurrence Biopsy
Positive
Surgically resect primary tumor with Mediastinal dissection. Consider additional radiation therapy and chemotherapy
Follow patient for local control, toxicity, and survival

Objectives:

Primary Goal: Overall survival at 3 years.

Secondary goals:

1. Local recurrence free survival (LRFS).
2. Time to local recurrence (TTLR).
3. Grade 3 and above acute and/or chronic toxicities.
4. To evaluate predictive value of pre and post treatment PET scan in clinical outcome.

Introduction:

Lung cancer remains the most frequent cause of cancer death in both men and women in North America. There are over 1,000,000 new cases of lung cancer annually world-wide. Seventy-five percent of patients with bronchogenic carcinoma will be diagnosed with non-small cell lung cancer (NSCLC). Approximately 15-20% of NSCLC patients present with early or localized disease (1-2). The number of patients diagnosed with stage I NSCLC is expected to rise significantly in the next several decades due to widespread screening with spiral CT. Surgical resection using lobectomy with mediastinal lymph node dissection or sampling in stage I (T1-2, NO) NSCLC results in five-year survival rates of approximately 60-70% (1-2) and remains the treatment of choice for this population.

Primary radiotherapy for early stage non-small lung cancer is considered reasonable non-surgical therapy for patients who cannot tolerate surgery. Conventional fractionated radiotherapy (60–66 Gy in 1.8- or 2.0-Gy fractions) in these patients with stage I/II disease has resulted in 5-year local control rates of 30% to 50% and overall survival rates of 10% to 30% (3-4). Modern three-dimensional (3-D) conformal radiotherapy, however, may improve clinical outcome compared with two-dimensional radiotherapy (6). Several studies have reported a benefit from such a dose escalation, suggesting a dose-response relationship from the standpoint of both survival and local disease control in these patients (7, 8). Because early-stage NSCLC is not inherently a systemic disease at the time of diagnosis and because local control is poor after conventional radiotherapy, research directed toward improving survival should put more emphasis on improving local tumor obliteration.

The development of 3-D conformal radiotherapy (3-DCRT) and stereotactic ablative radiation therapy (SABR), allows precise targeting and delivery of radiotherapy. SABR for lung cancer utilizes elements of 3-DCRT and also incorporates a variety of systems for taking cancer motion into consideration and decreasing set-up uncertainty using image guided radiotherapy techniques (9). These systems allow reduction of treatment volumes facilitating hypofractionation with markedly increased daily doses (>10 GY) and a significantly reduced overall treatment time. The combination of multiple beam angles

to achieve sharp dose gradients, high precision localization and a high dose per fraction in extracranial locations are referred to as SABR. This approach delivers a high biological effective dose (BED) to the target while minimizing the normal tissue toxicities, this may translate into improved local control and survival.

Several studies have reported significantly improved local control and survival using SABR in patients with stage I lung cancer (10-14). Onishi et al (10) retrospectively evaluated results from a Japanese multi-institutional SABR study (18). Patients with Stage I NSCLC (n = 245; median age, 76 years; T1N0M0, n = 155; T2N0M0, n = 90) were treated with hypofractionated high-dose SABR in 13 institutions. Stereotactic three-dimensional treatment was performed using noncoplanar dynamic arcs or multiple static ports. A total dose of 18-75 gray (Gy) at the isocenter was administered in 1-22 fractions. The median calculated biologic effective dose (BED) was 108 Gy (range, 57-180 Gy). During follow-up (median, 24 months; range, 7-78 months), pulmonary complications of National Cancer Institute-Common Toxicity Criteria Grade > 2 were observed in only 6 patients (2.4%). Local progression occurred in 33 patients (14.5%), and the local recurrence rate was 8.1% for BED > or = 100 Gy compared with 26.4% for < 100 Gy (P < 0.05). The 5-year overall survival rate of medically operable patients was 88.4% for BED > or = 100 Gy compared with 69.4% for < 100 Gy (P < 0.05). Their data showed that hypofractionated high-dose SABR with BED < 150 Gy was feasible and beneficial for curative treatment of patients with Stage I NSCLC. For all treatment methods and schedules, local control and survival rates were better with BED > or = 100 Gy compared with < 100 Gy. Survival rates in medically operable, BED > or = 100 Gy were comparable to those of surgery.

In the United States, McGarry and Timmerman conducted phase I and phase II clinical studies using SABR with 60 Gy in 3 fractions without heterogeneity correction (54 Gy in 3 fractions heterogeneity correction) with in stage I and selected stage II NSCLC (15, 16). Based on recent RTOG data analysis, 60 GY without heterogeneity correction is equal to 54 GY with heterogeneity correction. They described 10 local failures in 47 patients treated with stereotactic radioablation; 9 of these local failures occurred at doses ≤ 16 Gy X 3 and only one occurred at higher doses While maximum tolerated dose (MTD) was not achieved in patients with T1 tumors, in the T2 group with tumors > 5 cm, 3 of 5 patients treated with 24 Gy X 3 fractions suffered a toxicity ≥ grade 3 (two patients with pneumonitis, one with tracheal necrosis). The MTD for this subset was therefore defined at 66 Gy (22 Gy X 3 fractions). In their late phase II study (14), they found that peripheral lesions can be subjected to higher BEDs, but treatment of centrally located lesions can be associated with considerable long-term toxicity. For the latter, grade 3-5 long-term toxicity can be as high as 46% due to proximity of critical structures such as bronchus, major vessels, heart, spinal cord, esophagus and tracheal compared with 17% in peripherally located lesions. The Radiation Therapy Oncology Group recently published the final result for SABR in early stage NSCLC (RTOG 0236, chaired by Timmerman) in which patients with peripheral non-small cell lung cancers are treated with 60 Gy in 3fractions (54 Gy in 3 fractions heterogeneity correction); because of concerns regarding tracheal and bronchial stenosis at this dose level, the protocol defines a bronchial exclusion zone of 2 cm around major bronchi down to the lobar

level; patients with central tumors within this bronchial exclusion zone are not eligible for the protocol. They reported 98% local control rate with promising survival and acceptable toxicity (12).

SABR is now an accepted treatment for medically inoperable patients with stage I lung cancer, and patients with operable stage I lung cancer are entered on clinical protocols. Comparable outcomes after SABR and surgery treatments have been reported recently by several groups in patients with stage I NSCLC (17-20). Based on promising data mentioned above, we believe that it is necessary to conduct a prospective study to compare SABR with surgery, the current standard of care for stage I operable NSCLC.

There are several common dose regiments of SABR, one is 40-50 Gy delivered in 4 consecutive days and another one is the RTOG 0236 study using 54 Gy in 3 fractions delivered in 2 weeks. Based on Dr. Onishi's report, a BED >= 100 GY is associated with better local control (91.9% vs 73.6%) and survival (88.4% vs 69.4%) compared with BED < 100 GY. However, a very high dose regimen such as RTOG 0236 is associated with unacceptable toxicity for centrally located lesions.

At the University of Texas MD Anderson Cancer Center, we have treated more than 1000 patients with early stage or recurrent NSCLC using 50 Gy in 4 fractions with heterogeneity correction in both peripherally and centrally located lesions (14, 21, 22). With 26 months median follow up (up to 78 months), the local control rate is higher than 95% with median survival of 60 months and toxicity is acceptable even in centrally located lesions when normal tissue tolerance is respected . There were – a few cases of grade III/IV chronic toxicity (skin reaction and brachial plexus neuropathy) at the beginning of our program. Dose volume constrains have been modified based on these clinical data. Our data indicated that image-guided SABR with respect of critical normal tissue dose volume constraints is crucial to achieving optimal tumor control and minimizing side effects.

As we know, lung cancer moves during the radiotherapy. Particularly for SABR, tumor motion must be taken into consideration due to the high dose per fraction. There are several options for motion management. 4-D CT simulation based treatment planning and volumetric image guided delivery has significantly improved accuracy of SABR and minimized target miss and normal tissue overdosing. Another image-guided SABR approach is on-board image tracking. Target position is verified prior to each fraction and tracked continually throughout treatment (23, 24).

In the current study, we will use SABR to treat stage Ia NSCLC to a total dose of 50 GY with 12.5 GY/fraction (BED: 112.5 GY) for centrally located lesions and 54 Gy in 3 fractions for peripheral lesions. We anticipate that this regimen will achieve improved local control with decreased acute and long term toxicities compared with conventional radiotherapy.

Modern treatment planning systems, including PET/CT and 4-D CT, on-board volumetric image or tumor motion tracking based SABR planning and delivery are required to determine appropriate treatment margins. Initially patients were randomized

to receive SABR or surgical resection. However, only 39 patients over 5 years were enrolled due to failure of treating physicians and patients to accept randomization. The study is now revised as a prospective single arm clinical trial of SABR in stage IA non-small cell lung cancer patients with the primary objective to evaluate the overall survival (OS) for stage I non-small cell lung cancer patients treated with stereotactic body radiotherapy (SABR). Overall survival, progression free survival at the primary site, disease specific survival, and toxicities will be analyzed and compared between these two modalities.

Patient Eligibility:

1. Histological confirmation of non-small cell cancer will be required by either biopsy or cytology. The following primary cancer types are eligible: squamous cell carcinoma, adenocarcinoma with or without BAC features, large cell carcinoma with or without neuroendocrine features, neuroendocrine carcinoma, bronchioloalveolar cell carcinoma, or non-small cell carcinoma not otherwise specified.

2. Eligible patients must have appropriate staging studies identifying them as specific subsets of the revised IASLC stage IA based on the following combination of TNM staging:

   T1a,N0,M0 or T1b,N0,M0

3. A PET/CT scan is required. Patients with hilar or mediastinal lymph nodes with short axis diameter < 1cm and no abnormal hilar or mediastinal uptake on PET will be considered N0. Patients with > 1 cm short axis diameter of hilar or mediastinal lymph nodes on CT or abnormal PET (including suspicious but non-diagnostic uptake) may still be eligible if directed tissue biopsy of all abnormally identified areas are negative for cancer. Solitary pulmonary lesions <u>≤6</u>mm will not be considered significant.

4. The patients must be considered a reasonable candidate for surgical resection of the primary tumor. Standard justification for deeming a patient medically operable based on pulmonary function for surgical resection of NSCLC may include any of the following: Baseline FEV1 > 40% predicted, post-operative predicted FEV1 > 30% predicted, diffusion capacity > 40% predicted, absent baseline hypoxemia and/or hypercapnia, exercise oxygen consumption > 50% predicted, absent severe pulmonary hypertension, absent severe cerebral, cardiac, or peripheral vascular disease, and absent severe chronic heart disease.

5. Patients must be ≥ 18 years of age.

6. The patient's Zubrod performance status must be Zubrod 0-2.

7. <u>Mandatory staging studies:</u> Must be done within 10 weeks prior to study entry

- PET/CT scan to include both lungs, the mediastinum, and adrenal glands; Primary tumor dimension will be measured on diagnostic CT and again on simulation CT.
- Mediastinoscopy or endobronchial ultrasound (EBUS) guided biopsy of the mediastinal lymph nodes is required for all patients.
- MRI or CT scans of brain if there are symptoms or signs suggesting brain metastases,
- Invasive Mediastinal Staging – All patients with CT and/or PET evidence of hilar (level 10) or mediastinal lymph nodes > 1.0 cm in the shortest diameter must be staged by either cervical mediastinoscopy, esophageal endoscopic ultrasound guided biopsy, or endobronchial ultrasound guided biopsy. For those patients with left-sided tumors with enlarged (greater than 1.0 cm in the shortest diameter) aortopulmonary window nodes, a lymph node biopsy must be obtained of aortopulmonary nodes by either extended mediastinoscopy, Chamberlain procedure, VATS approach, or ultrasound guided biopsy to ensure that the patient does not have N2 disease. At the time of cervical mediastinoscopy, esophageal endoscopic ultrasound guided biopsy, or endobronchial ultrasound guided biopsy the following nodal stations must be examined and biopsied, if present: ipsilateral nodal station 4, contralateral nodal station level 4 and the subcarinal nodes (level 7). Any lymph node in the superior mediastinum or anterior mediastinum for left-sided tumors measuring greater than 1.0 cm in the shortest axis on CT scan and/or PET positive must be identified and biopsied. These nodal stations must be evaluated and nodes from these areas must be sampled if they are present, otherwise, the surgeon should note (on the Operative Report submitted for this procedure) that these areas were inspected and no nodes were present. For patients to be eligible, any positive mediastinal or distant sites identified on PET scan must be biopsy negative.

8. Patients must sign a study-specific consent form.

9. Patients (men and women) of child bearing potential should use an effective (for them) method of birth control throughout their participation in this study.

Patient Ineligibility:

1. Patients with primary tumors > 3 cm.
2. Patients with well-differentiated neuroendocrine carcinoma (carcinoid tumor).
3. Direct evidence of regional or distant metastases after appropriate staging studies, or synchronous primary or prior malignancy in the past 3 years other than nonmelanomatous skin cancer or in situ cancer.
4. Previous lung or mediastinal radiotherapy.
5. Plans for the patient to receive other concomitant local therapy (including standard fractionated radiotherapy and surgery) while on this protocol except at disease progression.
6. Pregnant or lactating women, as treatment involves unforeseeable risks to the embryo or fetus.

7. Cannot achieve acceptable SABR planning to meet minimal requirement of target coverage and dose-volume constraints of critical structures (see RT techniques).

Linear Accelerator (Linac) based SABR:

Immobilization and simulation:

Patients will be evaluated for regularity of breathing, responsiveness to feedback guidance, breath-hold capability. Based on this evaluation, one of the following acceptable treatment delivery techniques will be selected according to the treating physician's discretion:

1. breath-hold with feedback guidance

2. gated treatment

3. ITV based free-breathing

A CT study taken using the same method of respiratory management as treatment will be required for treatment planning purposes. This includes 4DCT for free-breathing, gated or abdominal compression techniques or repeated breath-hold CTs for breath-hold techniques. Feedback guidance, visual and/or audio, will be used for all patients who would both benefit from and respond to training with the feedback devices.

Four-dimensional CT is method of acquiring a collection of 3DCTs each representing a different portion of the patients breathing cycle. 4DCT acquires data for all locations in the treatment area over a time equal to or greater than a full respiratory cycle while simultaneously monitoring respiration. This is commercially available from several vendors using either a CINE or Helical acquisition technique. For free breathing treatment techniques radiotherapy will be designed based on the path of tumor motion during the whole breathing cycle, or a subset for gated techniques. For breath-hold treatment techniques the target shall be determined from a series of breath-hold CTs acquired at the time of simulation.

1. All simulations are strongly recommended to be done on CT scanners capable of acquiring 4DCT image data sets. Intravenous contrast is encouraged to help distinguish centrally located tumor from adjacent hilar vessels as appropriate.

2. Each patient will be immobilized in the treatment position on a flat table according to institutional practice and imaged in the treatment position.

3. The imaging session should consist of acquisition of a 4DCT covering both lungs entirely as well as the entire treatment volume plus at least 5 cm.

4. If the tumor is observed to move more than 1 cm on the 4DCT (edge to edge at motion extremes) or if critical normal tissue sparing is of concern, respiratory gated treatment, either free breathing or breath hold, should be considered.

5. An extended range free breathing scan may be acquired at the same time to serve as an anatomical reference.

Target delineation for SABR:

Four-dimensional (4D) CT images are strongly recommended in all cases. A 5-mm margin was added to iGTV to account for set-up errors, thereby creating the PTV.

Gross Tumor Volume (GTV): PET-CT scans should be used for the staging purposes and a guide. The GTV should be delineated using a 4-D CT taken in treatment position. Gross tumor volumes (GTVs) were delineated by using maximum intensity projection of 4D CT and modified by visual verification at different breathing phases. The path of movement of the GTV during the respiratory cycle was the internal gross tumor volume (iGTV). Pulmonary extent of lung tumors should be delineated on lung windows settings. 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. The target lesion will be outlined by an appropriately trained physician.

Clinical Target Volume (CTV): CTV margin is set to zero.

Planning Target Volume 1 (PTV): iGTV plus 5 mm isotropic margin to take residual motion, set up, uncertainty into consideration. No additional margins were used between the PTV and the block edge.

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 cm below the inferior extent of the PTV.

Esophagus The esophagus will be contoured using mediastinal windowing settings 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 cm 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 using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus. This neurovascular complex 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 2nd rib. This contour is only required when the lesion is located in the upper lobe.

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 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. The following airways will be included according to standard anatomical relationships: the distal 2 cm of trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the bronchus intermedius, 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.

Chest wall/Skin: The skin and the chest wall outside lung will be contoured.

Treatment planning:

Three-dimensional conformal SABR or intensity-modulated radiotherapy (IMRT) or volumetric modulated radiotherapy (VMAT) plan should be optimized using 6 to 12 coplanar or non-coplanar 6-MV photon beams or two arcs. SABR will be prescribed to a dose of 50 Gy to the PTV between the 75% and 90% isodose lines, which are created via AAA, Pinnacle calculation algorithms with heterogeneity correction. Typically, the lower prescription isodose line is chosen when the proximity of critical normal structures mandated a compromise to the PTV, and therefore a higher dose to the tumor center and sharper dose gradients are required. Normal tissue dose-volume constraints are based on BED calculations and our previous clinical findings of the toxicity of SABR and are shown in Table 1. It is required that the prescribed isodose line cover 100% of the IGTV in all cases. Typically, when the tumor was close to a critical structure, a compromise in PTV coverage is considered acceptable. In any situation, however, the iGTV plus a margin of 5 mm was required to receive at least 95% of the prescribed

dose and at least 95% of the iGTV plus a margin of 5 mm should receive at least the prescribed dose. Patients with lesions very close/ abutting to critical structures and whose normal tissue dose volume constraints, except for preferred dose volume constraints, can't be achieved should be removed from protocol.

Treatment Delivery

Daily imaging using in-room CT or linac-based cone beam CT (CBCT) will be required before each fraction. Adjustment of patient position is needed if target coverage is not adequate and/or critical normal tissues toxicity is a concern. Particularly, if the relationship between the GTV and the nearby boney anatomy moves beyond the PTV, the position is required to be re-adjusted and confirmed by repeated on-board CT.

a. The patient is initially set up based on simulation skin marks. The patient is then shifted to be approximately at the final isocenter in the longitudinal (sup-inf) and vertical (AP) direction, the lateral position is left at zero to facilitate CT imaging.

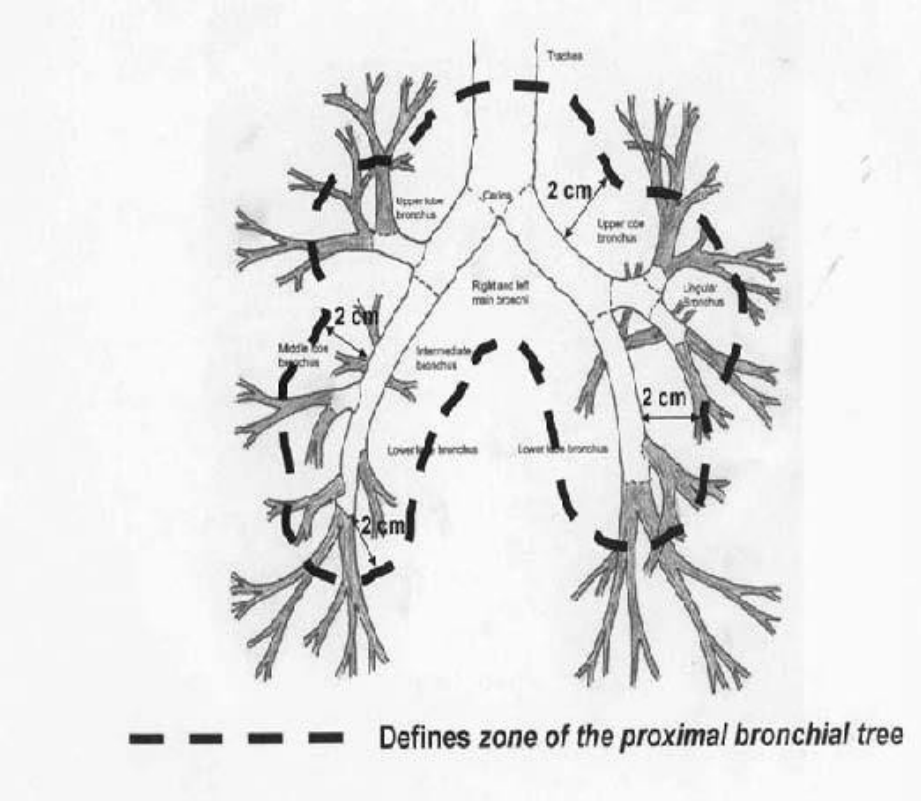
b. CT images are acquired either free breathing or breath-hold and these are used to determine a couch shift to cover the GTV.

c. The couch is shifted to the determined coordinates daily (for 4 fraction treatments) and orthogonal projection images are taken and shifts are verified based on bony anatomy as compared with DRRs (shifts away from boney anatomy to cover the GTV are factored into this evaluation). If any disagreement is identified the CT acquisition shall be repeated.

SABR Dose Specification:

Peripheral lesion:

Patients with peripherally located lesions, defined as located more than 2 cm away using the CT lung window level in all directions around the proximal bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus, right and left lower lobe bronchi (See figure 2), major vessels, esophagus, heart, tracheal, vertebral body, pericardium, mediastinal pleural and brachial plexus,



will receive SABR for a total dose of 54 GY calculated using the Monte Carlo comparable algorithm and CT heterogeneity correction with 18 Gy/fraction for a total of 3 fractions of radiation. The SABR dose is prescribed to the highest isodose line which is required to cover 100% of the GTV and more than 95% of the PTV (GTV + 5 mm). 100% of the PTV volume coverage by at least prescribed GY is encouraged. Higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. Treatment is recommended to be delivered on consecutive days. To consider some unanticipated issues such as holidays, machine down time, patient hospitalizations, and travel difficulty, treatment interruption will be allowed, but it should be completed within 12 days. It will be considered a minor deviation if treatment is delivered within 14days and a violation if longer than 14days.

<u>It is crucial that all critical organ dose-volume limits are evaluated and respected.</u>

Organ	Volume	Dose (cGy)
Spinal Cord	Any point	18 Gy(6 Gy per fraction)
Esophagus	Any point	27 Gy (9 Gy per fraction)
Ipsilateral Brachial Plexus	Any point	24 Gy (8 Gy per fraction)
Heart/Pericardium	Any point	30 Gy (10 Gy per fraction)
Trachea and Ipsilateral Bronchus	Any point	30 Gy (10 Gy per fraction)

Whole Lung (Right & Left, subtracting GTV)	Mean Lung Dose (MLD) V20 Gy V10 Gy V5 Gy	<= 5 Gy (preferred) <10%(of volume,preferred) <15% (preferred) <20% (preferred)
Skin Chest wall	<= 1 cc <= 50 cc(<=30cc preferred)	35 Gy (11.7 Gy/fx) 35 Gy (11.7 Gy/fx)

Table 1: Critical Organ Dose-Volume Limits for peripheral lesions

The table 1 lists maximum dose limits to a point or volume within several critical organs. **These are absolute limits except for preferred dose volume constraints, and treatment delivery that exceeds these limits will constitute a major protocol violation.** The dose is listed as total over 3 fractions and per fraction. If dose volume constraints of critical structures conflicts with required dose coverage of target volume, priority should be given to keep these dose volume constraints. However, 100% of the GTV volume must receive at least the prescribed dose (hot spots within GTV are allowed), ≥95% of the PTV volume must receive at least the prescribed dose, otherwise, it will constitute a major protocol violation. If these conditions cannot be met, the patient should be excluded from this protocol.

Central lesion:

Patients with a centrally located lesion, defined as located within 2 cm but more than 0.5 cm away using the CT lung window level of the bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, bronchus intermedius , right middle lobe bronchus, lingular bronchus, right and left lower lobe bronchi), major vessels, esophagus, heart, tracheal, pericardium, mediastinal pleural and brachial plexus and 1 cm away from the spinal canal, will receive SABR for a total dose of 50 GY calculated with Monte Carlo comparable algorithm and CT based heterogeneity correction with 12.5 GY/fractions for a total of 4 fractions. This dose is prescribed to the highest isodose line which is required to cover 100% of the GTV and more than 95% of the PTV (GTV + 5 mm). 100% of the PTV coverage by at least the prescription dose is encouraged.

Higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. Treatment is recommended to be delivered on consecutive days. To consider some unanticipated issues such as holidays, machine down time, patient hospitalizations, and travel difficulty, treatment interruption will be allowed but it should be completed within 5 days. It will be considered a minor deviation if treatment is delivered within 12 days and a violation if longer than 14 days.

The dose delivered to all important organs should be kept in the dose volume constraints as showed below:

Critical organ dose-volume constraints for central lesions:
It is required that spinal cord must be at least 5 mm away from 35 Gy isodose line.

	Volume	Dose (cGy)
Esophagus	Dmax <= 1 cc	35 Gy (8.8 Gy/fx) 30 Gy (7.5 Gy/fx)
Brachial Plexus	Any point <= 0.2cc	<35 Gy 30 Gy (7.5 Gy/fx)
Trachea	<= 1 cc	35 Gy (8.8 Gy/fx)
Main bronchus and bronchial tree	<= 1 cc	35 Gy (8.8 Gy/fx)
Heart	Dmax <= 1 cc <= 5 cc	45 Gy (11.25 Gy/fx) 40 Gy (8.8 Gy/fx) 20 Gy (5 Gy/fx, preferred)
Whole Lung (Right & Left, subtracting GTV)	MLD V20 GY V10 GY V5 GY	<= 5 Gy (preferred) <10% (of volume,preferred) <15% (preferred) <20% (preferred)
Major vessels	Dmax <= 1 cc	<=56 Gy 40 Gy (10 Gy/fx)
Skin Chest wall Spinal cord	<= 1 cc <= 50 cc (<=30 cc preferred) Dmax	35 Gy (8.8 Gy/fx) 35 Gy (8.8 Gy/fx) <25 Gy (6.25 Gy/fx)

Table 2: Critical Organ Dose-Volume Limits for central lesions. The table is modified based on our previous publications (22,23)

These are absolute limits except for preferred dose volume constraints, and treatment delivery that exceeds these limits will constitute a major protocol violation. The dose is listed as total over 4 fractions and per fraction. If dose volume constraints of critical structures conflicts with required dose coverage of target volume, priority should be given to keeping these dose volume constraints. However, 100% of the GTV volume must receive at least the prescribed dose (hot spots within GTV are allowed), ≥95% of the PTV volume must receive at least the prescribed dose, otherwise, it will constitute a major protocol violation. If these conditions cannot be met, the patient should be excluded from this protocol.

Chemotherapy after SABR:

Adjuvant Chemotherapy after SABR is not permitted for clinical stage IA patients.

Salvage surgery after SABR:

For a patient who has persistent or recurrent local disease after SABR as demonstrated by CT and/or PET and confirmed by biopsy after SABR, salvage surgical resection should be considered if the patient still can tolerate it. We will consider post-operation radiotherapy and chemotherapy for a positive margin or pathological N1 and N2.

Pre-treatment evaluation:

A complete history and physical to include performance status and concurrent non-malignant disease and its therapy must be recorded.

Laboratory studies will include a CBC with differential, platelet count, LFTs, electrolytes, creatinine.

Chest X-ray (optional), MRI or CT scans of brain should be performed if signs or symptoms of brain metastases are noted. A PET/CT scan within 10 weeks prior to study entry is required. All patients must have the mediastinum stage by EBUS or mediastinoscopy.

PFTs including FEV1, DLCO, TVC, FEV should be obtained within 10 weeks prior to study entry. A xenon study is recommended to evaluate the patient's tolerance for surgical resection.

Prescription Dose	Monte Carlo comparable Algorithm
Peripheral Lesions	54 Gy in 3 fractions
Central Lesions	50 Gy in 4 fractions

Table 3: Summary of prescription doses

Treatment evaluation:

Acute radiation reactions including esophagitis, pneumonitis and other adverse events will be evaluated during the period of treatment. The adverse events will be graded according to National Cancer Institute (NCI) Common Toxicity Criteria (CTC, V3). Only grade III and above toxicity will be recorded and analyzed.

Post-treatment evaluation:

	6 months	12 months	18 months	2 years	3 years	4 years	5 years
H & P	**X**	**X**	**X**	**X**	**X**	**X**	**X**
PET-CT	**X (Recommended but not required)**						
CT	**X (only if PET/CT not done)**	**X**	**X**	**X**	**X**	**X**	**X**
PFT		**X (Recommended but not required)**					

All timepoints are defined as +/- 1 month

Patients will be followed according to the table above following treatment. The first point of follow up will be at 6 months after treatment consisting of a history and physical exam and CXR if clinically indicated. PET-CT scanning is recommended but not required at the 6-12 month follow up period. All patients will undergo a CT scan at the 6 month follow up. If PET-CT is not performed at the 6-12 month follow up period, then a CT scan of the chest is required. PFTs are also recommended but not required during the 12 month follow up period. CT scans are required at the 12 month, 18 month, 24 month, 3 year, 4 year and 5 year follow-up encounters. All CT scans should be performed with IV contrast if possible. Interpretation of imaging studies for each patient by a single radiologist is strongly encouraged. It is strongly recommended that a single radiologist be appointed to coordinate the interpretation of all imaging studies for this protocol. Each of the above follow up points should be accompanied by a history and physical exam. For all follow up points except the 4-6 week following period, timing of +/- 1 month from the stated time period will be accepted.

Progression free survival at the primary site will be evaluated by the serial CT scanning as described in the follow up table above. Two years PFS will be calculated. PET information will be considered for calculation of PFS for distant metastasis and local recurrence.

Disease specific survival will be evaluated. Grade 3 and above acute and chronic toxicities by Common Toxicity Criteria will be analyzed.

RESPONSE	CT MASS SIZE (RECIST)	CT MASS QUALITY	PET*
COMPLETE (Two of the following)	Lesion disappearance (scar) or less than 25% of original size	Cyst cavity formation Low density	SUV<2.5
PARTIAL (One of the following)	More than 30% decrease in the sum LD of target lesions	Mass central necrosis or central cavity with liquid density	Decreased SUV or area of FDG uptake
STABLE LESION (One of the following)	Less than 30% decrease in the sum LD of target lesions	Mass solid appearance, no central necrosis or cavity	Unchanged SUV or area of FDG uptake
PROGRESSION (Two of the following)	Increase of more than 25% in sum LD of target lesions	Solid mass, invasion adjacent structures	Higher SUV (>5) or larger area of FDG uptake more than 6 months after SABR should promote biopsy (24)

Response assessment and calculation of PFS at the primary site:

Modified from the RECIST criteria (20, 21) *. (Target lesions= tumors treated; Sum LD= sum of the largest diameter (LD) of target lesion; SUV= standard uptake value of 18-FDG in PET scan).

Evaluation of Non-Target Lesions	
Marginal Failure **(MF)**	Refers to a measurable tumor located in the same lobe after SRT and within 2.0 cm of the treated PTV that has been confirmed with PET with uptake of a similar intensity as the pre-treatment staging PET, or confirmed by biopsy.
Regional Failure **(RF)**	Refers to a measurable tumor within lymph nodes along the natural lymphatic drainage typical for the location of the treated primary disease with dimension of at least >1.0 cm in the short axis on imaging studies (preferably CT scans) within the lung, bronchial hilum, or the mediastinum. Equivocally appearing enlarged lymph nodes should be positive on PET imaging or biopsied to confirm involvement with carcinoma.
Metastatic Dissemination **(MD)**	Refers to the appearance after protocol therapy of cancer deposits characteristic of metastatic dissemination from non-small cell lung cancer. Appropriate evaluations for making this determination include physical examination and imaging studies. PET scan or biopsy to confirm MD is encouraged but not required.

Criteria for Removal from Protocol Treatment

All reasons for discontinuation of treatment must be documented. All patients will be followed until death or 3 years post-treatment (whichever time point comes first) even though they are removed from protocol treatment.

1. Disease progression at any time during therapy or the follow up period; the patient should be re-staged and sites of recurrence and/or progression documented. Re-biopsy is strongly encouraged.
2. Development of unpredictable, irreversible, or persistent non-hematological grade 4 toxicity.
3. The patient may elect to withdraw from study treatment at any time for any reason.
4. Development of intercurrent, non-cancer related illnesses that prevent either continuation of therapy or regular follow up.

STATISTICAL CONSIDERATIONS

Sample Size Justification

The primary endpoint is overall survival. From the historical data of 229 patients treated with surgery, the 3-year OS rate was 85.5% (median OS time of 13.27 years). We expect that treatment of SABR will achieve similar therapeutic results. We will treat 80 patients with an anticipated accrual rate of 2 patients per month. Originally 20 patients entered in the first STARS randomized trial were to be included. However, these 20 patients were included in a combined randomized clinical trial analysis recently published in Lancet Oncology (Chang et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomized trials, Lancet Oncology, 2015). Twenty additional patients will be entered in the study as the original 20 patients include many from other institutions where it will be difficult to obtain current follow-up and to avoid publishing results from the same patients in more than one paper. To achieve the sample size of 80 treated patients, we would want to inflate the maximum sample size to 90 to account for the potential patients who are enrolled but not treated for ineligibility reasons.

All patients will be followed for a minimum of 3 years or until death. The final analysis will be performed when the last patient accrued in the trial is followed for 3 years, even if the total number of patients on the SABR arm is less than 80 patients. With 80 patients in the trial, a two-sided 95% confidence interval (CI) for the 3-year OS rate will extend ±7.7% from the observed rate for an expected rate of 85.5% (nQuery7.0). The final conclusion will be based on a 95% CI of the adjusted hazard ratio of OS computed from a Cox proportional hazards regression model including the potential confounding covariates given the study is not a randomized trial(27,28). Non- inferiority is claimed if the 3-year OS rate is not lower than the historical arm by more than 12%. The corresponding hazard ratio between the SBRT arm and the historical arm for the 3-year OS rate of 73.5% vs. 85.5% is 1.965. The upper bound of the observed 95% CI for HR less than 1.965 would lead to a conclusion of non- inferiority of SBRT to surgery. On the other hand, we will not claim that SBRT is non- inferior to surgery if the upper bound of the observed 95% CI for HR is greater than 1.965.

Trial Monitoring for OS

We will monitor the primary endpoint, OS, in the trial. The first of two interim analyses will occur when a total of 40 patients have accrued. The second interim analysis will occur when the 60^{th} patient accrues. Interim analysis will be deferred if insufficient events have occurred. At both interim analyses trial accrual will stop for predicted non-inferiority if there is at least 99% predictive probability of non- inferiority assuming the currently accrued patients are followed for an additional three years. Similarly, accrual will stop for futility if this predictive probability is less than 1%. These conservative boundaries have negligible effects on the trial's operating characteristics.

Analysis Plans

The primary efficacy endpoint is overall survival. The secondary endpoints include local recurrence free survival and time to local recurrence. OS will be measured from the start of treatment until death. LRFS will be measured from the start of treatment until the first date that local recurrence is objectively documented or death due to any cause, and patients without local recurrence or death will be censored at the last date when recurrence status is checked. TTLR will be measured from the start of treatment until the first date the local recurrence is objectively documented, and patients without local recurrence will be censored at the last date when recurrence status is checked. The Kaplan-Meier method will be used to estimate OS and LRFS(25). The method of Gooley, et al. will be used to estimate TTLR with death as a competing event(26). Complete response rate and overall response rate will be estimated with their 95% confidence intervals. Complete response rate and overall response rate will be estimated with their 95% confidence intervals.

We will conduct a risk-factor matched comparison study of the outcome (overall survival, progression-free survival, pattern of failure, grade 3 and above toxicities) between the current protocol and our institutional database using modern video-assisted thoracoscopic surgery (VATS) for stage I NSCLC (Stephens et al: Europe Journal of Cardio-Thoracic Surgery, 1-7, 2014, doi:10.1093.). We realize that selection bias between the current single arm trial and the VATS group will inherently present in this analysis. Besides the regular analysis we may also perform the propensity score matched (PSM) analysis to reduce the impact of the selection bias on the estimation of the primary endpoint, overall survival (OS), between the two groups. We will first decide on the set of potential confounding variables such as age, tumor size, etc., to be used for the matching. We will then identify patients from the two groups at a ratio of 1:1 or 1:2 using a 5 to 1 digit greedy match algorithm. We will use Fisher's exact test or Chi-square test to evaluate the association between categorical variables. We will use t-test or Wilcoxon rank sum test to evaluate the difference in a continuous variable between patient groups. Kaplan-Meier method will used for time-to-event outcome (including OS, LRFS, etc.) analysis, and log-rank test will be used to assess the difference in time-to-event outcome between patient groups. Multivariable Cox proportional hazards models will be used for multicovariate analysis to include important and significant covariates. To quantify the risk of developing progression event, we will use the cumulative incidence function counting death without progression (local recurrence, regional recurrence, or distant mets) as competing risk. To compare cumulative incidence functions, we will use Gray's test. The multivariable proportional hazards models of Fine and Gray may be used.

Safety:

Primary endpoint:

The primary safety endpoint is the occurrence of acute and late treatment-related grade 3 or 4 toxicity (per CTCAE, v.3.0) related to specific symptoms, including:

- Gastrointestinal: dysphagia, esophagitis, esophageal stricture, esophageal ulceration
- Cardiac: pericarditis, pericardial effusion, cardiomyopathy, ventricular dysfunction
- Neurologic: myelitis, neuropathy - cranial and motor
- Hemorrhage: pulmonary or upper respiratory

- Pulmonary: decline in pulmonary function as measured by pulmonary function tests, pneumonitis, pulmonary fibrosis, hypoxemia, pleural effusion or any grade 4 or 5 toxicity attributed to the therapy.

Secondary endpoint:

Toxicity frequency will be tabulated by most severe occurrence.

ADVERSE EVENT REPORTING

Adverse events will be reported in accordance with all applicable FDA, or regional/local governmental laws, ICH, and IRB rules, regulations, and guidelines including the International Standards Organization (ISO) 14155 and the Medical Devices (MEDDEV) guidelines. All adverse events regardless of toxicity grade and assigned treatment will be recorded in the appropriate online databases. Adverse event data will be analyzed and submitted to appropriate regulatory agencies per local regulations.

References:

1. Mountain CF. A new international staging system for lung cancer. Chest. 89:225-233, 1986.
2. Naruke T, et al. Prognosis and survival in resected lung carcinoma based on the new international staging system. J Thorac Cardiovasc Surg. 96: 440-447, 1988.
3. Kaskowitz L, et al. Radiation therapy alone for stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 27: 517, 1993.
4. Dosoretz DE, Katin MJ, Blitzer PH, Rubenstein JH, Galmarini DH, Garton GR, Salenius SA. Medically inoperable lung carcinoma: The role of radiation therapy. Sem Radiat Oncol. 6(2):98-104, 1996.
5. Sibley GS, Jamieson TA, Marks LB, Anscher MS, Prosnitz LR. Radiotherapy alone for medically inoperable stage I non-small cell lung cancer: The Duke experience. Int J Radiat Oncol Biol Phys. 40(1): 149-54, 1998.
6. Fang L, Komaki R, Allen P, et al. Comparison of outcomes for patients with medically inoperable Stage I non-small-cell lung cancer treated with two-dimensional vs. three-dimensional radiotherapy. Int J Radiat Oncol Biol Phys 2006, 66, 108-116.
7. Dosoretz D, et al. Radiation therapy in the management of medically inoperable carcinoma of the lung: Results and implications for future treatment strategies. Int J Radiat Oncol Biol Phys. 24:3, 1992.
8. Dosoretz DE, Galmarini D, Rubenstein JH, et al. Local control in medically inoperable lung cancer: An analysis of its importance in outcome and factors determining the probability of tumor eradication. Int J Radiat Oncol Biol Phys. 27(3): 507-16, 1993.
9. Chang JY, Roth JA. Stereotactic body radiation therapy for stage I NSCLC. Thoracic Surgery Clinics 17:251-259, 2007.
10. Onishi H, Araki T, Shirato H, et al: Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer. 2004 Oct 1;101(7):1623-31.
11. Nagata Y, Takayama K, Matsuo Y, et al. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. Int J Radiat Oncol Biol Phys. 63(5):1427-31, 2005.
12. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA. 2010; 303:1070–1076.
13. Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol. 2009; 27:3290–3296.
14. Chang JY, Liu H, Balter P, et al. Clinical outcome and predictors of survival and pneumonitis after stereotactic ablative radiotherapy for stage I non-small cell lung cancer. Radiat Oncol. 2012; 7:152.
15. McGarry RC et al. Stereotactic body radiation therapy of early-stage non–small-cell lung carcinoma: phase I study. Int. J. Radiation Oncology Biol. Phys. 63(4): 1010–1015, 2005
16. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive Toxicity When Treating Central Tumors in a Phase II Study of Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Lung Cancer. J Clin Oncol 24(30):4833-4839, 2006.

17. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SABR) for operable stage I non-small-cell lung cancer: can SABR be comparable to surgery? Int J Radiat Oncol Biol Phys. 2011; 81:1352-8.
18. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non small-cell lung cancer. J Clin Oncol. 2010; 28:928–935.
19. Crabtree TD, Denlinger CE, Meyers BF, et al. Stereotactic body radiation therapy versus surgical resection for stage I non small cell lung cancer. J Thorac Cardiovasc Surg. 2010; 140:377–386.
20. Shirvani SM, Jiang J, Chang JY, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. Int J Radiat Oncol Biol Phys. 2012; 84:1060-1070.
21. Chang JY, Balter PA, Dong L, et al. Stereotactic body radiation therapy in centrally and superiorly located Stage I or isolated recurrent non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2008; 72:967–971.
22. Chang JY, Liu H, Balter P, Komaki R, Liao Z, Welsh J, Mehran RJ, Roth JA and Swisher SG. Clinical outcome and predictors of survival and pneumonitis after stereotactic ablative radiotherapy for stage I non-small cell lung cancer. Radiation Oncology 7(1):152, 2012. e-Pub 9/2012.
23: Chang JY, Xu, Q, Li Q et al: Stereotactic ablative radiotherapy for centrally located early stage or isolated parenchymal recurrences of NSCLC: How to fly in a “no fly zone”. J Thoracic Oncology, in press.
24. Zhang X, Liu H, Balter P, et al. Positron emission tomography for assessing local failure after stereotactic body radiotherapy for non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2012; 85(5):1558-1565.
25. Kaplan EL and Meier P. Nonparametric estimation from incomplete observations. Journal of the American Statistical Association, 53:457-481, 1958.
26. Gooley TA, Leisenring W, Crowley J, and Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Statistics in Medicine, 18:695-706, 1999.
27. Rothmann M, Li N, Chen G, Chi GYH, Temple R, and Tsou HH. Design and analysis of non-inferiority mortality trials in oncology. Statistics in Medicine, 2003; 22:239-264.
28. Cox DR. Regression models and life tables (with discussion). Journal of the Royal Statistical Society B 1972; 34:187-220.

APPENDIX A – Performance Scales

KARNOFSKY PERFORMANCE SCALE:

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

ZUBROD PERFORMANCE SCALE:

0	Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50- 60).
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
5	Death (Karnofsky 0)

APPENDIX B - Revised Lung Cancer Staging IASLC Lung Cancer Staging Project

Regional Lymph Nodes

Direct extension of the primary tumour into lymph nodes is classified as lymph node metastasis.

Anatomical Subsites

1. Main bronchus (C34.0)
2. Upper lobe (C34.1)
3. Middle lobe (C34.2)

4. Lower lobe (C34.3)

Regional Lymph Nodes

The regional lymph nodes are the intrathoracic, scalene, and supraclavicular nodes.

TNM Clinical Classification

T – Primary Tumour

TX Primary tumour cannot be assessed, *or* tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

T0 No evidence of primary tumour

Tis Carcinoma in situ

T1 Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[1]

- T1a Tumour 2 cm or less in greatest dimension
- T1b Tumour more than 2 cm but not more than 3 cm in greatest dimension

T2 Tumour more than 3 cm but not more than 7 cm;
or tumour with *any* of the following features*:
- Involves main bronchus, 2 cm or more distal to the carina
- Invades visceral pleura
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

- T2a Tumour more than 3 cm but not more than 5 cm in greatest dimension
- T2b Tumour more than 5 cm but not more than 7 cm in greatest dimension

*T2 tumours with these features are classified T2a if 5 cm or less

T3 Tumour more than 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; *or* tumour in the main bronchus less than 2 cm distal to the carina[1] but without involvement of the carina; *or* associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe

Anatomical Subsites

1. Main bronchus (C34.0)
2. Upper lobe (C34.1)
3. Middle lobe (C34.2)

4. Lower lobe (C34.3)

Regional Lymph Nodes

The regional lymph nodes are the intrathoracic, scalene, and supraclavicular nodes.

TNM Clinical Classification

T – Primary Tumour

TX Primary tumour cannot be assessed, *or* tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0 No evidence of primary tumour
Tis Carcinoma in situ

T1 Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[1]
- T1a Tumour 2 cm or less in greatest dimension
- T1b Tumour more than 2 cm but not more than 3 cm in greatest dimension

T2 Tumour more than 3 cm but not more than 7 cm;
or tumour with *any* of the following features*:
- Involves main bronchus, 2 cm or more distal to the carina
- Invades visceral pleura
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T2a Tumour more than 3 cm but not more than 5 cm in greatest dimension
T2b Tumour more than 5 cm but not more than 7 cm in greatest dimension

*T2 tumours with these features are classified T2a if 5 cm or less

T3 Tumour more than 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; *or* tumour in the main bronchus less than 2 cm distal to the carina[1] but without involvement of the carina; *or* associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe

T4 Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe

N – Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M – Distant Metastasis

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
- M1a Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural (or pericardial) effusion[2]
- M1b Distant metastasis

Notes: 1. The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1.

2. Most pleural (and pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as T1, T2, T3 or T4.

pTNM Pathological Classification

The pT, pN, and pM categories correspond to the T, N, and M categories.

pN0 Histological examination of hilar and mediastinal lymphadenectomy specimen(s) will ordinarily include 6 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

G Histopathological Grading

GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Stage Grouping[#]

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a, b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a, b	N1	M0
	T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1, T2	N2	M0
	T3	N1, N2	M0
	T4	N0, N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

M1a	Separate tumour nodule(s) in a contralateral lobe;pleural nodules or malignant pleural (or pericardial) effusion
M1b	Distant metastasis

[#]The Stage Groupings (namely Stages I and II) are undergoing additional analysis and an addendum will be issued if necessary.