International randomized study to compare CyberKnife® Stereotactic Radiotherapy with surgical resection in stage I non-small cell lung cancer

Lung Cancer STARS (Stereotactic Radiotherapy vs. Surgery) Trial

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Objectives:

Primary Goal: To compare overall survival at 3 years

Secondary goals:

1. To compare disease specific survival at 3 years.
2. To compare 3 year progression free survival at the treated primary tumor site
3. To compare 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 body radiation therapy (SBRT), allows precise targeting and delivery of radiotherapy. SBRT 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 SBRT. 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 SBRT in patients with stage I lung cancer (10-12). Onishi et al (10) retrospectively evaluated results from a Japanese multi-institutional SBRT 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 SBRT 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 SBRT 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 SBRT with 60 Gy in 3 fractions without heterogeneity correction in stage I and selected stage II NSCLC (13, 14). 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 completed patients accrual for SBRT in early stage NSCLC (RTOG 0236, chaired by Timmerman) in which patients with peripheral non-small cell lung cancers are treated with 20 Gy X 3; 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.

SBRT 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.
Based on promising data mentioned above, we believe that it is necessary to conduct a
phase III randomized study to compare SBRT with surgery, the current standard of care
for stage I operable NSCLC.

There are several common dose regiments of SBRT, one is 40-50 Gy delivered in 4
consecutive days and another one is the current RTOG study using 60 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 220
patients with early stage or recurrent NSCLC using 50 Gy in 4 fractions with
heterogeneity correction in both peripherally and centrally located lesions (15-17). With
close to 18 months median follow up (up to 40 months), the local control rate is higher
than 95% and toxicity is minimal even in centrally located lesions. There were three
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. Since then, there have been no new cases of grade 3 and above
toxicities. Our data indicated that image-guided SBRT 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 SBRT, tumor
motion must be taken into consideration due to the high dose per fraction. There are
several options for motion management. CyberKnife system (Accuray Inc., Sunnyvale,
CA) is an intelligent robotic stereotactic radiosurgery system (SRS) which delivers high
dose radiation from hundreds of unique angles using a small X-band linear accelerator
mounted on a robotic arm. Target position is verified prior to each fraction and tracked
continually throughout treatment using two ceiling mounted x-ray guidance cameras
visualizing the target by creating bilateral 45 degree orthogonal images. The robotic arm
can move at a speed of several centimeters per second, which allows it to keep up with
tumor motion due to breathing. The CyberKnife was the first FDA approved clinical
radiosurgical system to use real-time motion compensation and has been shown to track
tumor motion in lung cancer and achieve promising tumor control (18, 19).

In the current study, we will use Cyberknife to treat stage I NSCLC to a total dose of 60 GY
with 15 GY/fraction (BED: 112.5 GY) for centrally located lesions and 60 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, are recommended to determine appropriate treatment margins. Patients will be randomized to receive Cyberknife SRT or surgical resection. Overall survival, progression free survival at the primary site, disease specific survival, and toxicities will be analyzed and compared between these two modalities. Patients who are randomized to surgery but who refuse this treatment and choose CyberKnife will be treated according to the protocol criteria for the CyberKnife arm of this protocol. These patients will be identified as “non-randomized” and will be analyzed separately from the randomized patients in this study.

**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 or IB based on only one of the following combinations of TNM staging:
   - T1, N0, M0
   - T2 (≤ 4 cm), 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 ≤ 4mm 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. **Mandatory staging studies:** Must be done within 8 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
• 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 > 4 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 5 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. Can not achieve acceptable SRT planning to meet minimal requirement of target coverage and dose-volume constraints of critical structures (see RT techniques).
Surgery:

Both open thoracotomy and video assisted thoracotomy (VATS) are acceptable procedures. Surgery may consist of a lobectomy, sleeve resection, bilobectomy or pneumonectomy as determined by the attending surgeon based on the operative findings. The type of resection chosen should provide complete removal of the primary lesion with negative gross and microscopic margins. Documentation of margins (bronchial and vascular and any other required) by frozen sections at surgery is recommended. Limited resection including wedge or segmental resections should not be performed unless there are unforeseen problems at the time of surgery.

All accessible hilar (level 10) lymph nodes must be dissected from the specimen by the surgeon and submitted to the pathologist. A complete mediastinal lymph node sampling should be performed for each patient. For right-sided lesions, this includes 4R, 7, and 9. For left-sided lesions, this includes 5, 6, 7, and 9.

Post surgery treatment:

Post-operative adjuvant chemotherapy will not be permitted if there is no lymph node involvement in the final pathological stage. We will consider post-operation radiotherapy and chemotherapy for a positive margin or pathological N1 and N2.

CyberKnife Radiotherapy:

Fiducial placement, simulation, target volume delineation and treatment planning

Fiducial placement: Patients in this protocol should have 1–5 gold fiducials implanted inside the tumor or in the vicinity of tumor for targeting purposes except for patients who are eligible for the fiducialless “x sight” option. It is recommended that at least 1 gold fiducial should be implanted inside the gross tumor. In addition, fluoroscopy or 4-DCT should be performed to confirm that the fiducials move with the tumor. The fiducials may be placed via either 1) percutaneous needle placement using an 18-19 gauge coaxial needle under imaged guidance and local anesthesia or 2) bronchoscopically by utilizing a bronchoscope in the usual standard fashion, or 3) endoscopically utilizing endoscopic ultrasound techniques in the usual standard fashion. Similar to fine needle biopsy, it is possible that placement of the fiducials may result in pneumothorax. If warranted, pneumothorax will be treated with needle aspiration and/or chest tube placement and evacuation. General patient care, respiratory care and chest tube management will be followed according to general routine protocol or as deemed appropriate by the investigator. To reduce the incidence of pneumothorax, bronchoscopy guided fiducials placement is preferred. Post-procedure chest x-rays and/or CT scans will
be taken of the chest prior to discharge, to detect any untoward parenchymal lung injury or occult pneumothoraces. Information specific to the fiducial placement procedure, locations and numbers of fiducials placed, treatment intervention, length of stay, duration of chest tube drainage (where applicable), and complications will be recorded onto case report forms.

Patient with peripheral lesion with tumor size > 1.5 cm that can be visualized by X-ray will be eligible for fiducialless “X sight” Lung option. The treating physician needs to verify that this “X sight” option is acceptable based on the treatment planning and the first day’s treatment to take uncertainty into consideration.

Simulation: CT simulation will be performed with the patient in the treatment position >2 days after fiducial placement (to enable resolution of edema and injury that may have occurred during fiducial placement and to allow for fiducial stabilization).

Computed Tomography (CT) will be the primary image for targeting and treatment planning. The planning CT scans must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting and is advised to be done with and without 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. The contrast free scan, registered by CT coordinates, is the recommended dataset for dose calculations. Axial acquisitions with gantry 0 degrees with spacing ≤ 1.5 mm between scans is recommended and spacing less than 3.0 mm between scans is required.

A CT simulation study will be required for treatment planning purposes. 4-dimensional (4-D CT) is a method of acquiring views of the tumor and surrounding anatomy at all stages of the respiratory cycle. 4-D CT is strongly recommended to verify that the fiducial system moves with the tumor and evaluate the tumor shape variation during the breathing. In the case of “X sight”, 4-D CT allows visible tumor position verification throughout its range of motion. The Cyberknife treatment will be designed based on 4-D images if available.

If 4-D CT is not available, fast (spiral) CT simulation should be used and appropriate techniques must be applied to improve identification of the target without motion artifact. The image of the end of expiration and the end of inspiration should be used to evaluate tumor deformation during the breath cycles and to contour the implanted fiducials without motion artifact.

Immobilization: Patients are recommended to be immobilized to reduce the uncertainty in the delivery of the treatment. An arms up position should be evaluated to allow the maximum number of beam angles but this needs to be balanced against patient comfort for potential long treatments. Commercially available immobilization device such as Alpha Cradle or Vac-Loc, combined with a wing board or other similar devices should be used to aid in immobilization.
Figure 1:

**Gross Tumor Volume (GTV):** PET-CT scans should be used for the staging purposes and a guide. The GTV should be delineated using a CT taken in treatment position. 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.

**Planning Target Volume 1 (PTV1):** includes the GTV plus a margin for the most probable location of high density clonogenic cell extension beyond the GTV, plus a margin for set-up and tracking uncertainty. PTV1 is defined as GTV + 3 mm isotropic margin.

**Clinical Target Volume (CTV):** This includes the GTV plus a larger margin to account for possible low density clonogenic cell extension to relatively large distances from the tumor. CTV is defined as GTV plus 8 mm margin edited as necessary to account for physical boundaries. CTV should not extend beyond anatomic boundaries such as vertebral body or any mediastinal structures. A physician should delineate the CTV.

**Planning Target Volume1 (PTV2):** CTV plus 3 mm isotropic margin to take residual motion, set up, fiducial uncertainty into consideration. Daily set up will be verified by image and daily breathing variation will be individually evaluated and adjusted using Synchrony.
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 (which ever 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.

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.

Treatment planning:

CT simulation images will be imported into the CyberKnife treatment planning system. A radiosurgical treatment plan will be then generated based on tumor geometry and location. All radiosurgery treatments will be administered using motion tracking techniques.

Three-dimensional isocentric or non-isocentric beam arrangements will be custom designed for each case based on the size and location of the lesion. Higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. Plans will be optimized and dose calculations will be performed using the ray tracing dose calculation algorithm. For data review purposes only, dose calculation using Monte Carlo dose algorithm should be submitted when this option is available. Based on recent data analysis, a correction factor of 1.2 provides approximate equivalence between Ray Tracing and Monte Carlo dose calculation algorithms when treating in lung with the CyberKnife System. For practical purpose, the ray tracing dose calculation algorithm will be used for this protocol and the 1.2 correction factor has been taken into consideration for the proposed dose regimens and should be considered when comparing the results of this protocol to other studies. Heterogeneity correction using appropriate CT density models must be applied for dose calculation. Where available, a custom CT density model derived from measurements made on the users CT scanner.
should be used. Alternatively, a standard density model including corrections at least for air, lung, and water should be applied. A CT image acquired without IV contrast is required for treatment planning dose calculation (i.e. this is the primary image data-set). It is recommended that a second CT image with IV contrast should be acquired and registered to the primary image. Images with IV contrast can be used for target delineation. To facilitate the evaluation of therapeutic efficacy, side effects and tolerant dose of normal structures, the patient plan including CT datasets and beam arrangements shall be archived and available for retrospective analysis.

Monte Carlo dose calculation is required to confirm the target coverage for centrally located lesion with size less than 2 cm. For the Cyberknife centers who do not have access to Monte Carlo dose calculation, they should not enroll patients with central lesion < 2 cm until this feature is installed on their treatment planning system. For the CyberKnife centers who have access to Monte Carlo dose calculation, evaluation of the dose distribution with Monte Carlo dose calculation is required for central lesion < 2 cm to verify the dose coverage, i.e., 50 Gy using Monte Carlo calculation (60 Gy / 1.2 correction factor) is required to cover 100% of the GTV and more than 95% of the PTV1 (GTV + 3 mm). If the dose coverage is acceptable the plan should remain untouched. If the dose coverage is unacceptable the plan can be adjusted to improve the coverage based on the Monte Carlo dose calculation but the plan must be recalculated and prescribed based on the pencil beam dose calculation to ensure that the coverage and normal tissue constraints are also met with the pencil beam dose calculation. Both the Monte Carlo and the pencil-beam dose calculation must be reported.

The Stereotactic Radiotherapy Procedure:

The CyberKnife (CK) treatment will be initiated within 2 weeks of the planning treatment CT. On the day of CK treatment, the subject will be taken into the CyberKnife system treatment room and LEDs will be attached to the subject’s chest or the subject will be given a tight-fitting jacket with LEDs attached. The LEDs will assist the system to track the tumor throughout the respiratory cycle. The subject then will be set up in their custom immobilization cradle on the CyberKnife couch. X-rays will be taken with the CyberKnife System to ensure that the tumor is aligned in a manner consistent with the position in which the treatment plan CT image was taken. Fiducial locations in the images will be extracted and compared to the fiducial locations in the CT scans to estimate tumor movements. Once the tumor is properly aligned, SRT will be initiated. During the course of SRT, x-rays will continue to be taken periodically to ensure correct tumor alignment. The maximum allowed correlation model error should be less than 3 mm. Global alignment on the spine for bulk patient setup should be accomplished prior to tracking the tumor. This will ensure that patient’s position corresponds to the planning CT scan.

The Synchrony option is required in order to enroll patients in this clinical evaluation and shall be used for all patients on this study since the tumors targeted for treatment in this protocol will likely move more than 3 mm during the respiratory cycle. Respiratory
tracking will be incorporated by the use of the Synchrony option. The Synchrony option is an optional feature of the CyberKnife system in which CT acquisition and treatment irradiation are performed during breathing. A set of infrared emitters are attached to the patient’s chest and/or abdomen, and an optical tracking system is used to track the emitters, thus measuring the chest/abdominal movements. In parallel, the orthogonal x-ray imaging system locates the fiducials. The locations of the fiducials and emitters are used to develop a correlation model that estimates the fiducial locations based on chest/abdominal movements. The correlation model along with the continuous real-time data from the optical tracking system are used to update the robot on the fiducial locations in real time. The robot uses these instructions to track the tumor in real time, making continuous adjustments for respiratory motion, thus eliminating the need for breath-holds.
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 SRT for a total dose of 60 GY calculated using CT heterogeneity correction with 20 Gy/fraction for a total of 3 fractions of radiation. This dose is prescribed to the highest isodose line which is required to cover 100% of the GTV and more than 95% of the PTV1 (GTV + 3 mm). 100% of the PTV1 volume coverage by at least 60 GY is encouraged. In addition, PTV2 should be evaluated to make sure that more than 95% PTV2 is covered by at least the 50 Gy isodose lines (see Fig. 1). The 50 Gy is intended for microscopic disease. Higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. In addition, the maximal dose point must be within 30% of prescribed dose (i.e. less than 78 Gy). 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
It is crucial that all critical organ dose-volume limits are evaluated and respected.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Volume</th>
<th>Dose (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Cord</td>
<td>Any point</td>
<td>18 Gy (6 Gy per fraction)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Any point</td>
<td>27 Gy (9 Gy per fraction)</td>
</tr>
<tr>
<td>Ipsilateral Brachial Plexus</td>
<td>Any point</td>
<td>24 Gy (8 Gy per fraction)</td>
</tr>
<tr>
<td>Heart/Pericardium</td>
<td>Any point</td>
<td>30 Gy (10 Gy per fraction)</td>
</tr>
<tr>
<td>Trachea and Ipsilateral Bronchus</td>
<td>Any point</td>
<td>30 Gy (10 Gy per fraction)</td>
</tr>
<tr>
<td>Whole Lung (Right &amp; Left, subtracting GTV)</td>
<td>V20 Gy V10 Gy V5 Gy</td>
<td>&lt;20% (of volume) &lt;30% &lt;50%</td>
</tr>
<tr>
<td>Skin Chest wall</td>
<td>&lt;= 1 cc &lt;= 10 cc &lt;=100 cc</td>
<td>35 Gy (11.7 Gy/fx) 30 Gy (10 Gy/fx) 30 Gy (10 Gy/fx)</td>
</tr>
</tbody>
</table>

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

The table lists maximum dose limits to a point or volume within several critical organs. These are absolute limits, 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 PTV1 volume must receive at least the prescribed dose and ≥95% of the PTV2 volume must receive at least minimal dose of 50 Gy, 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 bronchus), major vessels, esophagus, heart, tracheal, pericardium, mediastinal pleural and brachial plexus and 1 cm away from the spinal canal, will receive SRT for a total dose of 60 Gy calculated with CT based heterogeneity correction with 15 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 PTV1 (GTV + 3 mm). 100% of the PTV1 coverage by at least 60
GY is encouraged. In addition, PTV2 should be evaluated to make sure that more than 95% PTV2 is covered by at least the 50 Gy isodose line. The 50 Gy is intended for microscopic disease. Higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. In addition, the maximal dose point must be within 30% of prescribed dose (i.e. less than 78 Gy). 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 6-10 days and a violation if longer than 10 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:**
The maximum dose to esophagus, major vessels, heart, trachea and main bronchus should be less than 50 GY. The maximum dose to spinal cord should be less than 25 GY. In addition, it is required that spinal cord must be at least 5 mm away from 35 Gy isodose line.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Volume</th>
<th>Dose (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>&lt;= 1 cc &lt;= 10 cc</td>
<td>35 Gy (8.8 Gy/fx) 30 Gy (7.5 Gy/fx)</td>
</tr>
<tr>
<td>Brachial Plexus</td>
<td>Any point &lt;= 1 cc &lt;= 10 cc</td>
<td>&lt;40 Gy 35 Gy (8.8 Gy/fx) 30 Gy (7.5 Gy/fx)</td>
</tr>
<tr>
<td>Trachea</td>
<td>&lt;= 1 cc &lt;= 10 cc</td>
<td>35 Gy (8.8 Gy/fx) 30 Gy (7.5 Gy/fx)</td>
</tr>
<tr>
<td>Main bronchus and bronchial tree</td>
<td>&lt;= 1 cc &lt;= 10 cc</td>
<td>40 Gy (10 Gy/fx) 35 Gy (8.8 Gy/fx)</td>
</tr>
<tr>
<td>Heart</td>
<td>&lt;= 1 cc &lt;= 10 cc</td>
<td>40 Gy (10 Gy/fx) 35 Gy (8.8 Gy/fx)</td>
</tr>
<tr>
<td>Whole Lung (Right &amp; Left, subtracting GTV)</td>
<td>V20 GY V10 GY V5 GY</td>
<td>&lt;20% (of volume) &lt;30% &lt;50%</td>
</tr>
<tr>
<td>Major vessels</td>
<td>&lt;= 1 cc &lt;= 10 cc</td>
<td>40 Gy (10 Gy/fx) 35 Gy (8.8 Gy/fx)</td>
</tr>
<tr>
<td>Skin Chest wall Spinal cord</td>
<td>&lt;= 1 cc &lt;= 10 cc</td>
<td>40 Gy (10 Gy/fx) 35 Gy (8.8 Gy/fx) 30 Gy (7.5 Gy/fx) 20 Gy (5 Gy/Fx) 15 Gy (3.8 Gy/Fx)</td>
</tr>
</tbody>
</table>

**Table 2: Critical Organ Dose-Volume Limits for central lesions**
These are absolute limits, 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 PTV1 volume must receive at least the prescribed dose and ≥95% of the PTV2 volume must receive at least minimal dose of 50 GY, otherwise, it will constitute a major protocol violation. If these conditions cannot be met, the patient should be excluded from this protocol.

Chemotherapy after SRT:

Adjuvant Chemotherapy after SRT is not permitted for stage I patients.

Salvage surgery after SRT:

For a patient who has persistent or recurrent local disease after SRT as demonstrated by CT and/or PET and confirmed by biopsy after SRT, 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-randomization evaluation:

A complete history and physical to include performance status, recent weight loss, percent of weight loss, 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, MRI or CT scans of brain should be performed if signs or symptoms of brain metastases are noted. A PET/CT scan within 8 weeks prior to definitive treatment is required. For patients with hilar and/or mediastinal lymph nodes < 1 cm short axis diameter and PET/CT scan is not definitive, mediastinoscopy, EUS, or EBUS is required to evaluate possible lymph node involvement.

PFTs including FEV1, DLCO, TVC, FEV should be obtained within 8 weeks prior to definitive treatment. A xenon study is recommended to evaluate the patient’s tolerance for surgical resection.
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:

<table>
<thead>
<tr>
<th></th>
<th>4-6 weeks</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
<th>2 Years</th>
<th>3 Years</th>
<th>4 Years</th>
<th>5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>H &amp; P</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET-CT</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**All timepoints except the 4-6 week timepoint 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 4-6 weeks after treatment consisting of a history and physical exam and CXR if clinically indicated. PET-CT scanning is recommended for those patients in the SRT arm, but not required, at the 6 month follow up period. All patients in the surgery arm will undergo a CT scan at the 6 month follow up. If PET-CT is not performed at the 6 month follow up period, then a CT scan of the chest is required. PFTs are also 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 at each site 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 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).  

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>CT MASS SIZE (RECIST)</th>
<th>CT MASS QUALITY</th>
<th>PET*</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPLETE (Two of the following)</td>
<td>Lesion disappearance (scar) or less than 25% of original size</td>
<td>Cyst cavity formation Low density</td>
<td>SUV&lt;2.5</td>
</tr>
<tr>
<td>PARTIAL (One of the following)</td>
<td>More than 30% decrease in the sum LD of target lesions</td>
<td>Mass central necrosis or central cavity with liquid density</td>
<td>Decreased SUV or area of FDG uptake</td>
</tr>
<tr>
<td>STABLE LESION (One of the following)</td>
<td>Less than 30% decrease in the sum LD of target lesions</td>
<td>Mass solid appearance, no central necrosis or cavity</td>
<td>Unchanged SUV or area of FDG uptake</td>
</tr>
<tr>
<td>PROGRESSION (Two of the following)</td>
<td>Increase of more than 25% in sum LD of target lesions</td>
<td>Solid mass, invasion adjacent structures</td>
<td>Higher SUV or larger area of FDG uptake</td>
</tr>
</tbody>
</table>

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).

<table>
<thead>
<tr>
<th>Evaluation of Non-Target Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marginal Failure (MF)</td>
</tr>
<tr>
<td>Regional Failure (RF)</td>
</tr>
<tr>
<td>Metastatic Dissemination (MD)</td>
</tr>
</tbody>
</table>
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

Study Design

This is a 2-armed randomized Phase III trial in which randomization is to either stereotactic body radiation therapy (R) vs surgical resection (S). The primary endpoint is overall survival (OS). The goal is to compare OS in the two arms, with particular attention to detecting whether the OS hazard ratio of either R to S or S to R is greater than 1.50. (Assuming exponential survival and that the better performing group’s 3-yr OS rate is 85%, this implies that the other group’s 3-yr OS rate is no greater than 78.35 %.). All deaths are counted in the primary OS endpoint, regardless of cause. No specific adjustments/analyses will be done for competing risks. The DSMB will be presented with cause-of-death tables by arm, and similarly for eventual publications.

Sample Size:

Assuming exponential survival, follow-up of 3 years after the last patient accrues to the trial, an accrual rate of 30 patients per month, two-sided significance level of 5% and 90% power to detect a hazard ratio of 1.50 assuming that the better performing group has 85% 3-yr OS implies a total sample size of 1030 patients.

Statistical analyses:

All analyses will be intention-to-treat with patients lost to follow-up censored as of their last visit. All patients will be followed and counted in the therapy to which they were assigned, even if they decline that therapy. It is only those patients who refuse (in writing) to have their outcomes count in the study’s conclusions who will not be included. These usually account for 1% or less of the patients. Such patients will be replaced.

Efficacy:

Primary comparison:

Overall survival (OS): Kaplan-Meier curves will be plotted and compared for the two arms. Statistical tests will be based on the logrank statistic. A Cox proportional hazards
regression model will be used to relate length of survival with treatment arm. Pretreatment covariates will include clinical stage (T1a, T1b, or T2a), tumor location (central or peripheral), and investigational center.

**Secondary comparisons:**

Time to local recurrence, time to regional recurrence, time to disseminated recurrence, and progression-free survival will be compared for the two treatment groups using the same analyses as for OS. The number and percentage of patients undergoing salvage surgery in the SRT arm will also be evaluated.

**Safety:**

**Primary comparison:**

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 comparisons:**

Toxicity frequency will be tabulated by most severe occurrence.

**Interim Analyses and Data Safety Monitoring Board:**

An independent Data Safety Monitoring Board (DSMB) will be formed and will meet semi-annually. Details of DSMB operations are available in the DSMB Charter (Appendix L). Interim analyses for safety and efficacy will be presented to the DSMB at each meeting. The first meeting to review study data will be held within 6 weeks of the fifth patient treated on the clinical study. For each of the efficacy endpoints, but with special attention to the primary endpoint of OS, the study statistician will calculate Bayesian predictive probabilities (22) of a statistically significant difference between the two arms at the final analysis (3 years after the 1030th patient enters the trial). If this predictive probability is greater than 99% then the trial will cease. If patients are still accruing to the trial at this time, then accrual will end. If accrual is complete at this time, and if all patients have been treated so there is no possibility of crossing over to the other treatment arm, then the results of the trial will be released to the trial investigators. These results may be published at this time, however, all patients in the trial will be followed for a minimum of 3 years.

**Data Security and Confidentiality:**

As an introduction to the Kika Medical computing environment data security and confidentiality, we describe the following:
1) Data Content. Data content is determined by our customers’ SOPs and is study specific. Kika Medical provides systems that encourage our customers to anonymize all patient data and to maintain confidentiality of study participants for Health Insurance Portability and Accountability Act (HIPAA) compliance.

2) Data Forms. All eCRFs (electronic Case Report Forms) are designed to be clear and concise. The forms facilitate data acquisition, management and ensure that only authorized personnel have the appropriate access to specific patient data. During design and implementation Kika Medical personnel may identify situations where patient anonymity, confidentiality or security may be compromised and will bring these to the customer’s attention and suggest appropriate solutions.

3) Data Access. All access to data is strictly controlled though carefully designed application and database security features as well as system software, hardware and network controls. All application and data access is logged in a 21 CFR 11 compliant audit trail.

4) Data Transmission. No patient data is transmitted “in the clear”. All data is transmitted and received using 128 bit SSL key encryption.

5) Data Ownership. All data is owned by our customers. At study closure all data is transferred to appropriate media and format, sent to our customer and then deleted from Kika Medical systems. All ancillary study information and customer property is either returned to the customer or destroyed.

6) Data Storage. All data is stored in a physically and electronically secure site. System access is monitored on a continual basis and “anti-hacker measures” are in effect. Data is backed up both on and off-site. Off-site storage is also physically secured.

7) Regulatory Compliance. The Kika application, Eventa 2, is 21CFR 11 (Electronic Records and Signatures) compliant.

8) SOPs. Data security and confidentiality related processes are described in Kika Medical’s Quality Management System (QMS) SOPs. Kika Medical creates, maintains and delivers its products and services in compliance with this ISO 9001 approved QMS. All Kika Medical staff undergo frequent training to ensure continual QMS compliance.

ADVERSE EVENT REPORTING

Adverse events will be reported in accordance with all applicable FDA, ICH, and IRB rules, regulations, and guidelines.
References:


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.

**Distant Metastasis**
The categories M1 and pM1 may be further specified according to the following notation:
- Pulmonary PUL
- Bone marrow MAR
- Osseous OSS
- Pleura PLE
- Hepatic HEP
- Peritoneum PER
- Brain BRA
- Adrenals ADR
- Lymph nodes LYM
- Skin SKI
- Others OTH

**R Classification**
The absence or presence of residual tumour after treatment is described by the symbol R. The definitions of the R classification are:
- RX: Presence of residual tumour cannot be assessed
- R0: No residual tumour
- R1: Microscopic residual tumour
- R2: Macroscopic residual tumour

**Lung (ICD-O C34)**

**Rules for Classification**
The classification applies only to carcinomas. There should be histological confirmation of the disease and division of cases by histological type.
The following are the procedures for assessing T, N, and M categories:
- **T categories**
  - Physical examination, imaging, endoscopy, and/or surgical exploration
- **N categories**
  - Physical examination, imaging, endoscopy, and/or surgical exploration
- **M categories**
  - Physical examination, imaging, and/or surgical exploration
**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)*

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 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
   M1b  Distant metastasis

Note: 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.
More pleural (and pericardial) effusions with long tumor are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is non-bloody and is not an effusion. 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 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
Stage IIB T2b N1 M0
Stage IIIA T3 N0 M0
Stage IIIB T4 N2 M0
Stage IV Any T N3 M0
Stage IV Any T Any N M1
M1a  Separate tumour nodule(s) in a contralateral pleural effusion
M1b  Distant metastasis

The Stage Groupings (namely Stages I and II) are undergoing additional analysis and an addendum will be issued if necessary.
APPENDIX C - REGISTRATION PROCEDURES for SRT

Pre-Registration Requirement

The Facility is required to have PET, CT, Cyberknife with Synchrony option.

Documented ability to transfer patient specific material and treatment planning parameters including CT-based dose deposition representations, dose-volume matrices and parameters, and stereotactic targeting representations to the MDACC (digital data submission).

Each institution will be required to submit a benchmark plan provided by the Radiological Physics Center (RPC) at MD Anderson Cancer Center that will be reviewed by the team at MDACC. The specifics of this review and the details of credentialing will be provided in a separate document.

Each institution must submit and successfully complete a protocol-specific Dry-Run Test, the treatment plan for the first patient to be treated at the site on this protocol PRIOR TO DELIVERING ANY PROTOCOL TREATMENT. The plan will be reviewed centrally at the MDACC, and suggestions regarding protocol compliance will be forwarded to the participating institution. The treatment plan for subsequent patients enrolled at a site will not be required to be centrally reviewed prior to treatment, but will be reviewed for protocol compliance at a later date.

Registration

Online Registration

Online (versus Dial-in) registration is mandatory for this study. Patients can be registered only after eligibility criteria are met. Patients will be registered online through a web based electronic database. A user name and password is required and will be unique to each user from each site. The case report forms will verify that the study candidate meets all of the eligibility criteria mandatory for a patient to be included in the study. Once this information is verified, the system will assign a patient ID to the patient and allow access to the study case report forms as well as to the randomization module described below.

Randomization

Online Randomization

Online (versus Dial-in) randomization of patients to one of the two treatment arms will be utilized for this study. Once a patient has met all of the eligibility criteria for inclusion in the study, a unique patient ID will be generated and the online 3rd party database will randomly assign the patient to one of the two treatment arms. Case report forms, specific to that assigned treatment arm will then be provided throughout the treatment and follow up periods for that patient.
Data Submission

Digital Data Submission

A third party vendor will be contracted that will provide a secure, HIPPA compliant database that will handle all registration of patients and capture of all of the data and variables for this study and its follow up. Each site will have a unique site ID and each patient will be assigned a unique ID. The online database will verify all patients meet the required eligibility criteria and a site has completed all of the required checklist items, such as informed consent, to allow enrollment of each patient. Selective access to view specific variables within the database will be granted to the Data Safety Monitoring Board for their review purposes, to the study monitoring team and to MDACC for their review of data and for the purposes of evaluating any possible protocol violations.

In addition to the variables collected on the case report forms by this electronic database, the planning and treatment parameters and planning images will be stored as well with an attached unique patient ID. This information will be submitted electronically via an FTP system to a central secure server within 1 week of the generation of this data.
Appendix - H.

Appendix Subtitle: Participating Sites List

1.) Advocate Christ Medical Center  
   Oak Lawn, IL 60453  
   FWA# 00000472

2.) Community Regional Medical Center - Fresno  
   Fresno, CA 93721  
   FWA# 00000927

3.) Jupiter Medical Center  
   Jupiter, FL 33458  
   FWA# 00004766

4.) Parkview Hospital  
   Fort Wayne, IN 46805  
   FWA# 00003435

5.) Saint Louis University  
   St. Louis, MO 63110  
   FWA# 00005304

6.) St. Joseph Mercy Hospital  
   Ann Arbor, MI 48106  
   FWA# 0000188

7.) St. Mary's Duluth Clinic Health System  
   Duluth, MN 55805  
   FWA# 00000635

8.) St. Mary's Medical Center  
   Huntington, WV 25702  
   FWA# 00002704

9.) Stanford University School of Medicine  
    Palo Alto CA. 94305  
    FWA# 00000935

10.) Central Baptist Hospital  
    Lexington, KY 40503  
    FWA# 00003601

11.) Tianjin Cancer Hospital  
    HeXi District Tianjin, 300060 P. R. China  
    FWA# 00013991
12.) Ruikang Hospital, Guangxi Traditional Chinese Medical University  
   10 Huadong Road  
   Nanning, 530011 P.R. China  
   FWA#A00014795

13.) St. Luke's Episcopal Hospital, Cancer Center at St. Luke's  
    Houston, TX 77030  
    FWA #00000286 (Baylor College of Medicine IRB)

14.) Penrose Cancer Center  
    Colorado Springs, Colorado 80907  
    FWA#00003978

15.) Taipei Medical University Municipal Wan Fang Hospital  
    Taipei, Taiwan  
    FWA# 00011022

16.) St Mary's of Michigan-Seton Cancer Institute  
    Saginaw, MI  
    FWA # 00004305