The GPS Trial

Calypso **G**uided High **P**recision **S**tereotactic Ablative Radiosurgery for Lung Tumours Using Real-Time Tumour Tracking & Respiratory Gating: A seamless Phase I/II prospective clinical trial.

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Table Of Contents

1.0 Study Schema

This trial is a seamless phase I/II prospective, single arm, cohort study.

Phase I of the trial will consist of two patients and will serve to conduct quality assurance assessments and to familiarize thoracic surgeons, radiation oncologists, and medical physicists at CancerCare Manitoba and Health Sciences Center in the use and work flow of the Health Canada approved endobronchial implanted real-time tumor tracking transponder beacons (The Calypso™ beacon). Patients in phase I will undergo standard stereotactic ablative radiotherapy (SABR) of a lung tumor with prior endobronchial transponder beacon placement. For phase I, the transponder beacons will be used for comparative localization analyses and SABR treatment setup procedures will be carried out independent of transponder beacon data, however, transponder data will be collected in order to conduct, post-treatment, *in vivo* quality assurance assessments of beacon performance characteristics. Otherwise, the SABR treatment for phase I will consist of the currently accepted standard internal target volume based and standard image guided SABR.

Phase II of this trial will consist of 26 patients who will undergo a specialized form of SABR radiotherapy specifically designed to take full advantage of the real-time tumor tracking ability of the Calypso™ transponder beacons. Specifically, SABR in phase II will consist of smaller radiotherapy treatment volumes employing respiratory gating and smaller planning target volume expansion margins given the superior tumor location telemetry afforded by the Calypso™ beacons. Comparative dosimetric analyses contrasting the traditional ITV/PTV style treatments to those with reduced ITV/PTV margins achieved via Calypso guided SABR will be performed. Patient self-reported quality of life and toxicity assessments will be collected with the goal of facilitating power and sample size calculations for the design of a larger phase III randomized controlled trial of Calypso guided SABR treatment in the future.

Phase I (n=2)

Adults ≥ 18 years of age
T1N0M0 or T2N0M0 (<4cm) NSCLC; or
A single Metastatic Lung Tumor < 4cm
ECOG performance status 0 to 2
Surgically inoperable
Non-Oxygen dependent at baseline

→

"Standard" Stereotactic Ablative Radiotherapy:

1) Endobronchial Calypso Beacon Placement
2) 4-Dimensional CT Simulation Scan
3) ITV based "standard" SABR planning with 5mm PTV Expansion margins
4) Image guided "Standard" SABR (54Gy/3#)
5) Quality Assurance measurements
6) Quality of Life and Toxicity Assessments

Phase II (n=26)

Adults ≥ 18 years of age
T1N0M0 or T2N0M0 (<4cm) NSCLC; or
A single Metastatic Lung Tumor < 4cm
ECOG performance status 0 to 2
Surgically inoperable
Non-Oxygen dependent at baseline

→

Calypso Guided Stereotactic Ablative Radiotherapy:

1) Endobronchial Calypso Beacon Placement
2) 4-Dimensional CT Simulation Scan
3) ITV-free and 2mm PTV margin SABR planning
4) Respiratory gated Calypso guided SABR (54Gy/3#)
5) Quality of Life and Toxicity Assessments
6) Radiotherapy dosimetry planning studies

Planned Sample Size: Phase I (n=2); phase II (n=26)

2.0 Background:

Stereotactic Ablative Body Radiotherapy (SABR)

Stereotactic Ablative Body Radiosurgery (SABR) is a modern radiotherapy technique which consists of the delivery of tumoricidal (ablative) doses of radiation to a tumor target inside the body. In contrast to conventional radiotherapy which delivers the total dose to the tumor over six to seven weeks with small daily doses of radiotherapy (2 Gy per fraction for 30 to 33 fractions), SABR is delivered using much larger ablative doses of radiotherapy per fraction (ranging from 8 to 34 Gy per fraction) allowing for the total dose to be delivered in a small number of fractions (1 to 5 fractions). With larger doses per fraction, and delivery of radiotherapy over a shorter period of time, SABR affords a larger biological effective dose of radiotherapy when compared to conventional fractionated radiotherapy. In general, most SABR dose regimens have biological effective doses in excess of 100Gy delivered with conventional fractionation.

To date, SABR has been utilized for the treatment of primary or metastatic tumors of the lung[1], prostate[2], spine[3], liver[4], and brain[5] offering excellent local disease control for patients who are either surgically inoperable or for those who refuse surgical management[6]. SABR of early stage non-small cell lung cancers offers local control rates of the target tumor in the range of 90 to 96% at three years following treatment[7]. By contrast, the use of conventional 3-dimensional conformal radiotherapy with doses as high as 70Gy with standard fraction sizes for early stage lung cancer yields considerably inferior results and only provides durable local control in 43% of cases[8]. Thus, from a lung tumor control standpoint for small lung tumors, SABR has become the most widely accepted choice of radiotherapy dose fractionation.

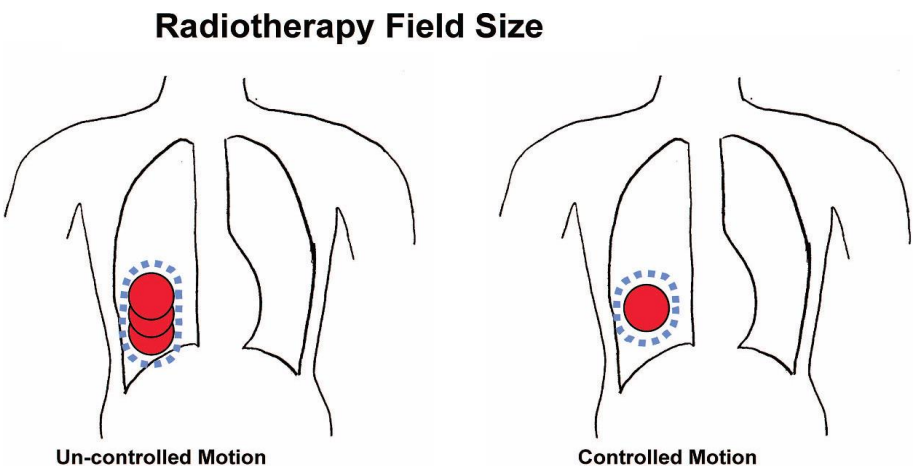
Motion Management Strategies for SABR of Lung Tumors

SABR treatment of lung tumors is challenging in that lung tumors are constantly in motion in multiple axes as a result of respiratory and cardiac motion. This motion creates considerable uncertainty in targeting the tumor during SABR treatment. In some cases, small lung tumors can have a respiratory motion path of upwards of 5 centimeters[9], especially amongst tumors which are located close to the diaphragm in the middle or lower lobes of the lungs[10], or for patients with poor pulmonary function with irregular breathing patterns.

Lung tumor motion has significant implications for radiotherapy treatment planning especially impacting the size of the margin added to the gross tumor volume (GTV) to encompass the moving tumor, and the amount of radiation dose delivered to normal thoracic organs at risk (such as the heart, normal lung tissue, chest wall, ribs, etc). In general, the more a lung tumor moves, the larger the radiotherapy treatment volumes required to encompass the motion and thus the greater the unwanted dose of radiotherapy to healthy OARs (Figure 1).

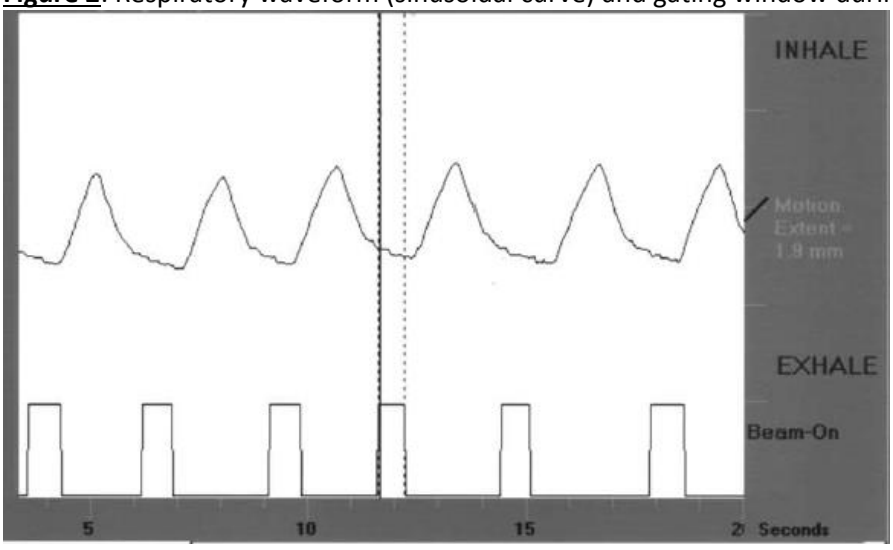
As such, many strategies have been employed to date in order to manage the motion of lung tumors undergoing SABR treatment including: respiratory gating, breath hold techniques (either deep inspiration, or end-exhalation), abdominal compression plates to force shallow breathing patterns, and motion encompassing strategies (4-Dimensional CT scans). Each of these motion management strategies has their distinct advantages and disadvantages in terms of dosimetric sparing of OARs, patient tolerability/practicality, and accuracy (see table 1).

Figure 1: The relationship between tumor motion and radiotherapy field sizes[11].



Respiratory gating consists of the delivery of radiation therapy during a pre-selected portion of the respiratory cycle (typically end-exhalation expiration, when the tumor is relatively still) which requires continuous monitoring with an external surrogate marker of breathing motion (such as the Varian RPM system). Respiratory gating (Figure 2) can potentially reduce dose to OARs by reducing the ITV and therefore the PTV volume, however it requires robust correlation of lung tumor motion to the motion of an external surrogate marker. However, this can be difficult for non-compliant patients, or for patients with irregular breathing waveforms. Respiratory gated SABR treatment also takes considerably longer to deliver (since radiotherapy is only delivered during 20 to 30% of each respiratory cycle), especially when using standard radiotherapy dose rates (600 MU/min) which can result in treatment durations as long as 60 minutes per fraction. However, with the advent of rapid radiotherapy dose rates of up to 2400 MU/min attainable using the latest linear accelerator designs (such as the Varian Edge™ at the KIAM) treatment times can be reduced to around 15 to 20 minutes, thus the problem of protracted treatment durations have largely been solved.

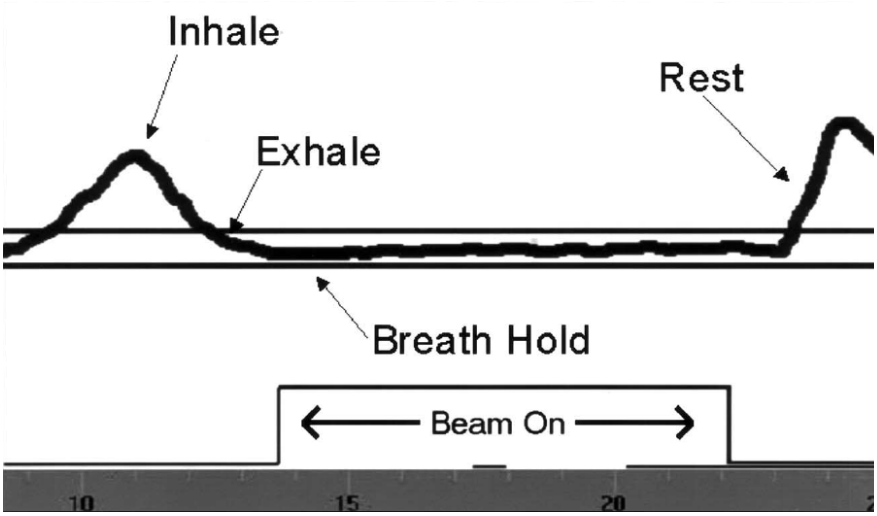
Figure 2: Respiratory waveform (sinusoidal curve) and gating window during end-exhalation[12].



Abdominal compression plates[13] to induce shallow breathing patterns and *breath-held techniques*[11] have the theoretical advantage of reducing dose to OARs by reducing the internal movement of the tumor.

Both methods have been studied extensively, but clinical enthusiasm for their use has largely waned due to concerns of poor tolerability by patients (especially amongst patients with poor pulmonary function and limited respiratory reserve), and the prerequisite of highly compliant and motivated patients.

Figure 3: The end-exhalation breath hold method of lung tumor motion management[12].



The most common forms of lung tumor motion management in clinical use today are motion encompassing methods. These techniques make use of four-dimensional CT simulation scans *(4DCT)* to provide 3D patient anatomy sampled at regular time points throughout the respiratory cycle. A 4DCT is a specialized radiotherapy CT simulation scan whereby the patient is scanned when comfortably free-breathing while their respiratory motion is continuously quantified using an external surrogate marker system (which consists of an infrared marker box placed on the abdominal surface of the supine patient, and its position is monitored continuously).

Both the CT data and the surrogate respiratory motion data are acquired simultaneously during the 4DCT scan which takes approximately 90 seconds to capture[14]. Specialized computer software is used to "bin" the scan's data into ten distinct respiratory-phase correlated CT datasets which represent the different phases of the respiratory cycle. Radiotherapy treatment planning software allows a radiation oncologist to delineate the gross tumor volume (GTV) on each of the ten phases of the respiratory cycle. These 10 GTVs are summed together (using a "merge structure" function) and the resultant structure, termed the the internal target volume (ITV) [15] represents all the regions of the lung in which the lung tumor *could be* at any given moment during the respiratory cycle. The advantage of the ITV based method is that it produces an "individualized" representation of the GTV to account for its internal movement in the body and therefore reduces the possibility of a geographic "miss" of the tumor during SABR. The disadvantage of this method of tumor delineation is that it can make for very large treatment volumes and lead to higher radiation doses to OARs. As a result of the ITV method, a generous portion of a patient's healthy lung tissues are ablated during SABR and so patients are subject to potential adverse effects due to radiation dose delivered to healthy organs at risk (OAR) nearby to the tumor (summarized in table 2).

Table 1: Overview of Current Lung Tumor Motion Management Strategies

Management Strategy	Advantages	Disadvantages
Respiratory Gating	-Potential to reduce OAR dose -No need for traditional ITV -Potential to reduce PTV volume when compared to ITV based approaches	-Protracted Treatment Durations (if using "slow" dose rates) due to low duty cycle (note: this is not an issue with the Varian Edge linear accelerator) -Dependent on external surrogate marker for tumor motion signal -Some patients are unable to breathe with a regular rhythm (anxiety)
Abdominal Compression plate	-Reduction in tumor motion due to forced shallow breathing -Reduced internal margin -Potential to reduce PTV volumes when compared to non-compression treatments	-Not well tolerated by patients due to discomfort -Difficult for patients with limited functional lung volumes to tolerate -Time consuming daily treatment setup
Motion Encompassing methods (4DCT scans)	-Well tolerated by patients -Can be employed for patients with poor pulmonary function	-Requires use of ITV, which increases treatment volumes (especially for tumors with large motion amplitude). -Dependent on external correlative surrogate for tumor motion
Breath hold technique	- Reduced internal margin -No need for ITV -Potential to reduce PTV volumes when compared to non-breath hold techniques -Potential to reduce OAR Dose	-Requires highly compliant patients - Difficult for patients with limited functional lung volumes to tolerate - Dependent on external correlative surrogate for tumor motion

Table 2: Common Complications to Thoracic Organs At Risk following Standard SABR treatments

Organ at Risk	Potential Complication	Risk
Lung	Pneumonitis (≥Grade 2)	10-20%[16-19]
Ribs	Rib Fracture	35%[20]
Chest Wall	Chest Wall Pain (≥Grade 2)	39%[21]

Real-time tracking of a lung tumor's location during SABR treatment would obviate the need to use a standard ITV-based approach for treatment planning and would serve to simultaneously improve the accuracy and precision of SABR while reducing the volume of healthy lung treated to an ablative dose of radiotherapy. Real-time tumor location telemetry data would allow the SABR radiation treatment beam to be automatically activated when the tumor is positioned within the desired target location in the thorax, and deactivated when the tumor moves outside of the chosen target location. This method of radiation treatment delivery is known as respiratory-gated[12] radiotherapy and it carries the potential benefit of reducing the planning target volume of the radiotherapy[22]. The dosimetric benefits of respiratory-gated radiotherapy depend mainly on the size of the target tumor (larger tumors benefit

more than smaller tumors) and the extent of the motion of the tumor (tumors with large amplitudes benefit the most and tumors with amplitudes <1cm do not seem to benefit in a meaningful way from respiratory gated therapy[10,23]). Since most patients undergoing SABR treatments are almost always surgically inoperable due to the presence of one or more respiratory comorbidities (emphysema, bronchiectasis, etc) with poor pulmonary function, minimizing the volume of functional normal lung tissue ablated along with the tumor is of critical importance.

SABR Treatment of Lung Tumors using Calypso Tracking Beacons

In 2016, a Varian Edge™ radiotherapy treatment machine (linear accelerator) was installed and commissioned at the Kleysen Institute for Advanced Medicine (KIAM) at the Health Sciences Center (HSC) in Winnipeg, Canada. This state of the art linear accelerator was specifically designed to deliver SABR treatments and is specially equipped with the Calypso™ lung tracking beacon system.

The anchored Calypso™ lung tracking beacon is a grain-of-rice sized transponder beacon (Figure 4) which is placed immediately adjacent to a lung tumor using a flexible bronchoscope. Typically three beacons are placed in the small airways of the lung (2 to 2.5 mm diameter airways) adjacent to the target tumor (within 3 cm of the tumor)[24]. The Calypso beacon can be used as either a traditional radiopaque fiducial marker (which can be identified using standard kilovoltage x-rays, fluoroscopy, or CT scans) or as a passive electromagnetic beacon transponder. Each beacon measures 2 mm in diameter and 8 mm in length (14mm including the anchoring legs) and consists of a miniature electrical circuit that is encapsulated in a sealed biocompatible glass capsule. In order to prevent the beacon from migrating within the airways, the beacon has an affixed five-legged anchoring system which expands to 5mm in diameter once deployed from the Calypso lung catheter. The Calypso transponder beacon is placed endobronchially using the working channel of a bronchoscope and the Calypso lung catheter (Figure 5). Navigational bronchoscopy can be used to pre-plan the optimal location for each beacon to be placed within the airways by using a pre-bronchoscopy CT scan.

FIGURE 4: The Calypso™ Anchored Transponder Beacon with legs completely constrained (left), and deployed (right).

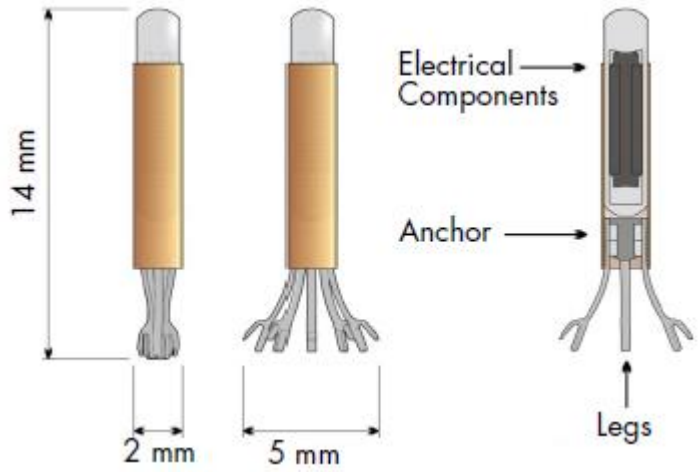
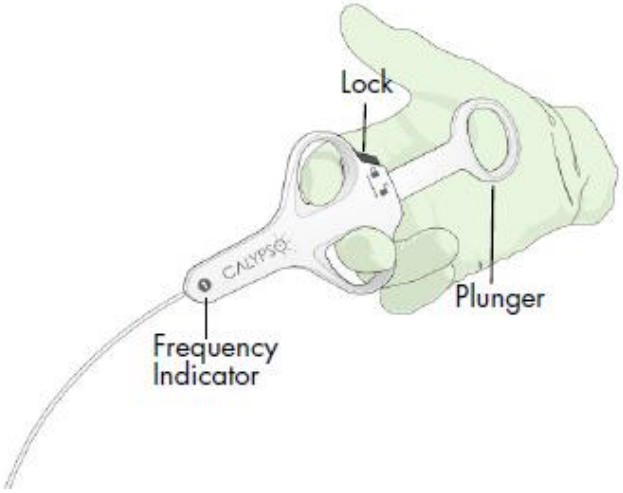
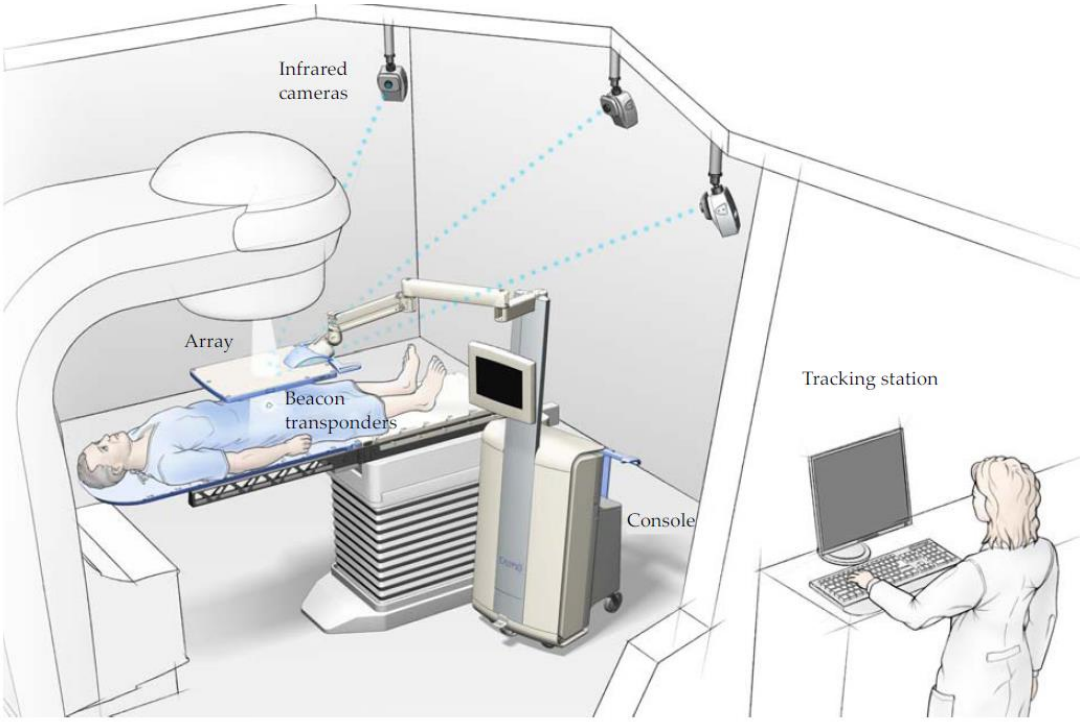


Figure 5: The single use Calypso Lung Catheter (for use in the working channel of a bronchoscope)



The transponder's electrical circuit is passive and the beacon does not contain an internal energy source. The transponder only emits a radiofrequency (RF) signal when it is excited by a harmless, non-ionizing RF field generated by the Calypso array (Figure 6). After RF excitation, each transponder briefly emits a response signal at a unique frequency that is specific to each beacon. This signal is detected by the sensor array with a refresh rate of 25 times per second (25 Hz). The Calypso system uses this information from all of the beacons to continuously determine the three dimensional location of the tumor isocenter relative to the linear accelerator's isocenter. This allows for real time monitoring of a lung tumor's motion during radiation treatment delivery.

Figure 6: Calypso system components



The Calypso lung beacon was recently granted Health Canada approval for routine endobronchial implantation in human patients following a phase I human study of the Calypso transponder beacon for patients with early stage lung cancer[24] which demonstrated excellent tolerability and safety.

In lay terms, the Calypso beacons function similarly to a GPS navigation device, only instead of locating the position of a person on a map, they locate the position of the tumor within the lung in real time at the time of SABR treatment. This real-time tumor position information permits very high accuracy SABR delivery to lung tumors with the potential for significantly smaller treatment volumes and therefore less acute or late SABR related toxicity.

Calypso beacons have been employed in other radiotherapeutic settings including prostate cancer [25] and liver cancer. In the case of prostate cancer patients treated with Calypso-guided radiotherapy, the improved accuracy and real-time tumor tracking allowed treatment PTV margins to be reduced to as small as 3mm, which in turn resulted in smaller PTV volumes, less toxicity to nearby organs at risk, and improved quality of life[25]. It is therefore expected that Calypso-guided radiotherapy could produce analogous beneficial results for patients undergoing SABR treatments for their lung tumors. To this end, we therefore propose this seamless phase I/II prospective clinical trial for patients with mobile tumors of the lungs undergoing SABR which will utilize the Calypso tracking beacon to enable end-exhalation gated,ITV-free radiotherapy treatment planning with minimal PTV margins. The integration of these treatment planning and SABR delivery features is anticipated to reduce radiotherapy treatment volumes, dose to OARs, with excellent tolerability and quality of life.

3.0 Trial Design

This is a prospective, single arm, seamless phase I/II cohort study (investigator initiated trial) with a planned total accrual of 28 patients.

4.0 Study Population:

Potentially eligible patients are adults with surgically inoperable, biopsy proven or suspected single T1N0 or T2N0 Non-small cell lung cancer tumor or patients with a single pulmonary metastasis (<4 cm maximal tumor dimension) from a known primary malignancy of any histology (either metastatic failure to a single pulmonary site after primary radical treatment, or metastatic progression to a single lung metastasis following palliative chemotherapy with no other sites of uncontrolled disease). Tumors should be located either in the lower lobe, lingula, or right middle lobe of the lung however, patients with upper lobe tumors are eligible as long as the tumors have a respiratory amplitude of ≥1cm. Tumors should be located at least 2 cm from the proximal bronchial tree (non-central tumors).

5.0 Eligibility Criteria:

1) Adult ≥ 18 years of age who is surgically inoperable, or refusing surgical management.
2) Tumor criteria (a patient must satisfy one of “a”, “b” below to be eligible):
    a. AJCC 7th edition clinical T1aN0M0, T1bN0M0, or T2aN0M0 (<4cm) Non-small cell lung cancer (adenocarcinoma, squamous cell carcinoma, or NSCLC Not Otherwise Specified) of the middle or lower lobes of the lung*;
    b. A single pulmonary metastasis (<4cm) of a known primary malignancy of any histology involving the middle or lower lobes of the lung* (either metastatic failure to a single pulmonary site after primary radical treatment, metastatic progression to a single lung

metastasis following palliative chemotherapy, or a single pulmonary metastatic lesion of newly diagnosed stage IV malignancy).

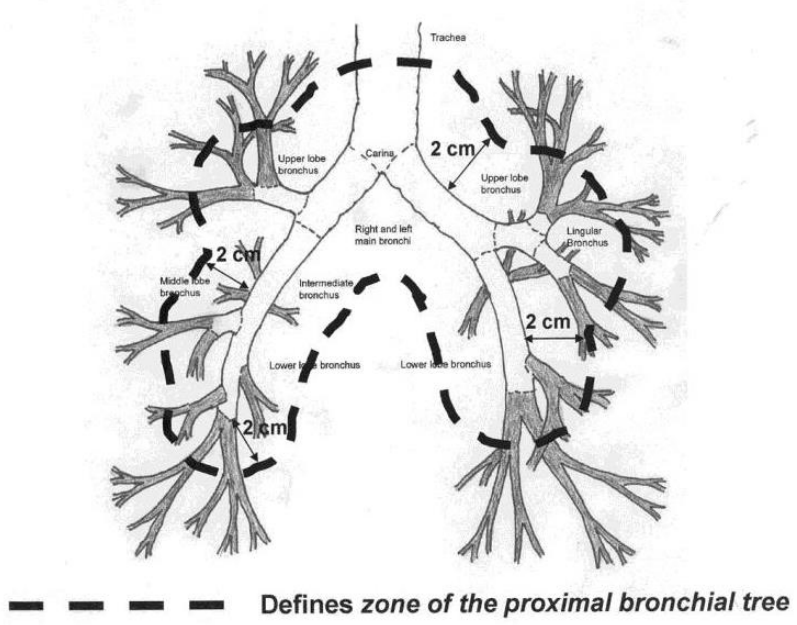
*upper lobe tumors are eligible for trial participation if the tumor has a demonstrated tumor motion of ≥1 cm in any axis (as assessed by fluoroscopy at the time of bronchoscopy).

3) Confirmation of malignancy (a patient must satisfy one of "a", "b" below to be eligible):
    a. Tumors accessible by bronchoscopy, image-guided percutaneous biopsy, or other invasive staging methods require biopsy confirmation of malignancy.
    b. If a tumor is not amenable to a diagnostic biopsy, evidence of growth of the target tumor on serial imaging scans is necessary prior to enrollment. An increase in SUV of the target tumor on serial PET scans is also acceptable.
4) ECOG performance status of 0 to 2.
5) Minimum life expectancy of 6 months.
6) Deemed fit to undergo bronchoscopy by their participating thoracic surgeon
7) Deemed fit to undergo SABR by their participating Radiation Oncologist.
8) Respiratory function (a patient must satisfy both "a" and "b" below):
    a. Minimum FEV1 of 0.8 liters
    b. Minimum DLCO of 35% predicted.
9) Able to provide written informed consent and understand verbal instructions necessary for radiotherapy treatments.

Exclusion Criteria:

1) Tumors located < 1cm from the chest wall based on CT imaging.
2) Tumors located ≤ 2 cm from the proximal bronchial tree (see figure 7)
3) Patients who require supplemental oxygen at rest.
4) Patients who are unable to lie flat or still for a minimum of 30 minutes.
5) ECOG performance status 3 or 4.
6) Evidence of uncontrolled extra-thoracic metastatic disease (based on imaging or clinical findings).
7) Proven or suspected intrathoracic lymph node involvement.
8) Prior SABR to the target tumor.
9) Prior history of idiopathic pulmonary fibrosis, interstitial lung disease, or active collagen vascular disease (systemic lupus erythematosus, Rheumatoid arthritis, or Scleroderma)
10) Pregnancy.
11) Active pulmonary infection
12) Known hypersensitivity to nickel titanium (Nitinol)
13) Known Bronchiectasis of the small airways nearest to the tumor

Figure 7: The proximal bronchial tree (tumous within this region are ineligible for trial participation).



6.0 Study Objectives:

Phase I:

1) To allow for members of the interdisciplinary care team (Thoracic surgeons, Radiation Oncology, Radiation Therapists, and Medical Physicists) to familiarize themselves with the clinical use of implanted endobronchial tumor tracking beacons and carry out quality assurance assessments in preparation for the subsequent phase II component of the study.
2) To quantify the presence (if any) of beacon migration (inter-beacon distance) at different time points in a patient's care path (time of implantation, CT simulation scan, and days of SABR treatment).
3) To assess the quality of life of patients having Calypso placement (EORTC QLQ - LC13 questionnaire)
4) To assess acute toxicity of beacon implantation using the Common Terminology for Criteria for Adverse Events (CTCAE version 4.0)
5) To quantify the potential benefit of continuous monitoring of tumor location using Calypso by comparing it to traditional imaging-based setup.

Phase II:

1) To quantitatively assess the differences in irradiated treatment volumes and radiotherapy dose volume metrics for the PTV and healthy thoracic organs at risk between Calypso™ guided respiratory gated SABR and the traditional ITV based radiotherapy.
2) To serially quantify the acute and late toxicity of patients undergoing Calypso™ guided SABR using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0
3) To serially quantify the self-reported quality of life of patients undergoing Calypso Guided SABR using the EORTC QLQ - LC13 questionnaire
4) To serially biobank blood and urine samples for patients undergoing radical SABR of lung tumors to allow for the future development of novel prognostic and predictive biomarkers for patients undergoing SABR.
5) To serially quantify changes to pulmonary function following SABR treatment

6) To demonstrate the benefit of Calypso treatments in reducing patient-specific component of PTV margins

Study Hypotheses:
Phase I: Calypso beacon placement will be safe and well tolerated and will function within their specified tolerances with minimal (sub-millimeter) inter-beacon migration.

Phase II: The Median Planning Target Volume (PTV) of Calypso guided respiratory gated SABR will be 40% smaller than the median PTV volume of standard ITV based SABR treatment with standard PTV margins. Furthermore, thoracic organs at risk will receive significantly less radiotherapy dose when compared to the standard SABR treatment.

7.0 Study Endpoints:

Primary Endpoints
Phase I: Mean difference in inter-beacon distance (in millimeters) (at time of 4DCT simulation compared to fractions 1,2, and 3 of SABR)

Phase 2: Mean within patient difference in PTV volumes of standard ITV-based SABR compared to gated SABR utilizing Calypso based PTV margins (expressed as a percentage difference).

Secondary Endpoints:
1) Patient self-reported quality of life (EORTC QLQ - LC13 questionnaire)
2) Acute and late toxicity - Common Terminology for Criteria for Adverse Events (CTCAE version 4.0)
3) Median within patient difference in radiotherapy doses to thoracic Organs at risk
4) Median change in FEV1, DLCO, and 6 minute walking distance on room air at baseline compared to follow-up time points.
5) Local tumor control (using the RECIST version 1.1 Criteria[26])
6) Progression Free Survival
7) Cancer Specific Survival
8) Overall Survival

8.0 Pre-treatment Investigations:
All staging investigations shall be completed within 12 weeks prior to study enrollment.
1) History and Physical Exam
2) CT scan or MRI of brain
3) PET scan
4) CT chest and abdomen
5) Pulmonary function testing (including spirometry, diffusion capacity, and 6 minute walk test)
6) CBC, electrolytes, BUN, Creatinine
7) Quantitative beta-HCG (Only if the participant is a premenopausal female).

9.0 Study Enrollment Procedures
Participating investigators are responsible for confirming the eligibility/ineligibility status of a potential study participant prior to enrollment. Since this trial requires the active participation of both thoracic

surgeons and radiation oncologists, a patient should be assessed by both specialists prior to being offered participation in the trial.

Potentially eligible patients will be offered voluntary participation in this trial by their participating physician. Patients will be given an informed consent form to review and will be contacted at a later date by trial personnel to answer any questions which may arise and to obtain written informed consent.

Patients who have consented to trial participation will then undergo all required pre-treatment investigations (if not already done) in a timely manner.

10.0 Treatment

Calypso Beacon Placement:

Calypso beacon placement will be performed using flexible bronchoscopy under general anesthesia or conscious sedation. The site of implantation will be localized using a combination of direct visualization, fluoroscopy, ultrasound and electromagnetic navigation bronchoscopy. Drs. Buduhan and Tan have received formal course training on the use of SuperDimension Navigational Bronchoscopy System for localization of lung nodules and directed bronchoscopic placement of implant devices. This will greatly facilitate accurate beacon placement. The bronchoscope will be advanced under direct vision into the targeted implantation site. Using navigational bronchoscopy and fluoroscopy the target implant sites will be identified and guide sheath placed through the bronchoscopy working channel. Through the guide sheath, the catheter with anchored beacon transponder will be directed to the implantation sites under bronchoscopic and fluoroscopic direction. The beacon transponders will be deployed until properly anchored in the appropriate peri-tumoral implantation sites. Satisfactory beacon placement will be verified using fluoroscopy. The anchored transponders are implanted in a triangle around the tumor target and are at least 1 cm but no more than 7.5 cm from each other. Although navigational bronchoscopy is recommended for beacon placement, conventional bronchoscopy with fluoroscopic guidance is also acceptable for beacon placement at the discretion of the attending thoracic surgeon in the event that navigational bronchoscopy is unavailable on the day of the beacon placement procedure.

Radiotherapy:

4-Dimensional CT simulation Scan: Patients will be simulated in the supine position and immobilized using a Vac-lok bag with arms raised above their heads and with legs on a knee rest for comfort. Patients will be free breathing with a relaxed tidal breathing pattern. The CT simulation scan will be performed using the Varian RPM system in order to produce 10-respiratory phase correlated CT data sets (4-DCT scan). Intravenous contrast is not required.

Co-registration of PET scan: For purposes of contouring the primary tumor, PET scan fusion is recommended but not mandatory.

Organ at Risk Delineation: The following organs at risk will be contoured on the $CT_{average}$ dataset:

1) Normal Lung;
2) Esophagus;
3) Chest wall (within 5 cm of the PTV);

4) Ribs (within 5 cm of the PTV);
5) Heart;
6) Kidneys (if the tumor is a lower lobe tumor);
7) Ipsilateral brachial plexus (if located within 5 cm of the PTV);
8) Spinal Cord;
9) Proximal Trachea;
10) Proximal bronchial tree;
11) Aorta (if left sided tumor);
12) Vena Cava (if right sided tumor);
13) Liver (if tumor is located in the right lower lobe)
14) Nearest vertebral body, and the vertebral body above and below the nearest vertebral body.

For organ at risk contouring guidelines, radiation oncologists are encouraged to reference the RTOG 0236 trial protocol.

Target Volume Delineation:
The Gross Tumor Volume (GTV) will be delineated on all 10 respiratory-phase correlated CT datasets with the CT Hounsfield unit window level set to the "lung window" preset. Participating radiation oncologists are encouraged to cross-reference the pre-treatment investigations (Infused CT chest, PET scan, etc) in order to aid with the delineation of the GTV.

Internal Target Volume: Using the average CT dataset, the ITV will be generated using the Eclipse™ "accumulate structure" function incorporating the GTVs created on all 10 phase-correlated datasets.

Gating Window Internal Target Volume (ITV_{GW}): The ITV_{GW} will consist of a accumulated structure composed of the GTVs contoured on the end-exhalation phases of the breathing cycle. The end-exhalation phases will typically include the GTVs from the CT50, CT40, and CT60 phases of the 4DCT scan. Depending on the individual patient's breathing pattern, the ITV_{GW} could also include the GTVs from CT30 and CT70 if necessary (this decision to include CT30 and CT70 needs to be approved by the study PI on a case-by-case basis).

Planning Target Volume expansion margins:
For Phase I of the study - 5 mm isotropic expansion of the ITV
For Phase II of the study - 3mm isotropic expansion of the ITV_{GW}.

Note: For patients treated in phase II of the study, If setup errors noted during the first fraction of treatment are greater than 3mm in size for more than 10% of the overall treatment time, then a larger, case-specific PTV margin will be applied for the remaining 2 fractions of the radiotherapy. Any enlargements to the PTV will be applied with the prior approval of the study PI.

Radiotherapy Dose Prescription: 54 Gy to 95% of PTV in 3 fractions.

Radiotherapy Dose Coverage: 99% of the PTV receives at least 90% of prescription dose

Timing of Fractions: A minimum of 40 hours should separate each fraction.

Radiotherapy treatment planning: SABR treatment plans will be calculated using the Varian Acuros dosimetric algorithm with inhomogeneity correction. Two co-planar, two-hundred and forty degree arcs of volumetric modulated arc therapy (VMAT) will be the default beam arrangement.

SABR Delivery: SABR will be delivered using the Varian Edge linear accelerator at the KIAM using 10MV flattening filter free photon beams using a dose rate of 2400 MU/min.

Gating Window: The end-exhalation phase (CT50) plus one phase directly preceding (CT40) and following (CT60) will used as the gating window. CT30 and CT70 may also be included in the gating window.

Chemotherapy: Chemotherapy, immunotherapy, or mutation targeted therapies should be held at least 24 hours prior to the first fraction, and can be restarted 24 hours after the delivery of the last fraction.

Cone Beam CT-based (CBCT) Image Guidance: In phase I of the trial, cone beam CT scans will be performed daily in order to allow for initial image guidance of treatment setup using bony landmarks (vertebral bodies) and soft tissue (tumour). Calypso beacon data will be collected during phase I including inter-transponder geometry.

Calypso Guidance: In Phase II of the trial, calypso beacon data will be used toe tine initial patient positioning and treatment delivery. The location data from the Calypso beacons will be captured by the Calypso array in order to assess inter-transponder beacon distance, as well as beacon geometric center location relative to the linear accelerator's isocenter. This position is used as the reference for Calypso to provide continuous monitoring. Calypso data will then be used for respiratory gating of the SABR treatment. CBCT imaging may also be performed to verify the soft tissue-beacon correspondence. CBCT images will be evaluated and may be used for patient repositioning if necessary.

Respiratory gating (phase I): For phase I of the trial, the respiratory gating signal will not be used to control the radiation beam delivery, however, Calypso transponder beacons will be used to provide location telemetry for quality assurance and data analysis purposes only.

Respiratory Gating (Phase II): The SABR radiation beam delivery will be gated using the Calypso transponder location data for phase II of the study.

OAR Tolerances (as derived from the RTOG 0618 protocol by Timmerman et. al.):

Organ	**Volume**	**Dose Constraint (Gy)**
Spinal Canal	Point Dose <0.35cc <1.2cc	19 Gy 18 Gy 10 Gy
Esophagus	Point Dose <5cc	28 Gy 15 Gy
Ipsilateral Brachial Plexus	Point Dose <3cc	24 Gy 22 Gy
Heart	Point Dose <15cc	30 Gy 24 Gy

Proximal Bronchial Tree	Point Dose <4cc	30 Gy 14 Gy
Skin	Point Dose <10cc	24 Gy 22 Gy
Ribs	Point Dose < 1cc	30 Gy 24 Gy
Chest Wall	Point Dose < 30 cc	30 Gy 20 Gy
Great Vessels	Point Dose <10cc	35 Gy 30 Gy
Stomach	Point Dose <10 cc	22Gy 15 Gy
Liver	>700cc	15 Gy
Bilateral Normal Lung	See section below	See section below
Bilateral Normal Lung	V20Gy	<10%

Dose Spillage and conformality:

High dose spillage: Any dose > 105% of the prescription dose should occur primarily within the PTV itself and not within normal tissues outside of the PTV. The cumulative volume of all tissues outside of the PTV receiving a dose of > 105% of the prescription dose should be no more than 15% of the PTV volume.

The falloff gradient beyond the PTV extending into normal tissue structures (especially the lungs) must be rapid in all directions and meet the following criteria which are dependent on the PTV volume as outlined in the table below: 1) The ratio of the volume of the 54 Gy isodose surgace to the PTV volume should be less than 1.2 (see column two of the table below); 2) The ratio of the volume of the 30Gy isodose volume to the volume of the PTV must be no greater than the "R_{30Gy}"(see column three in the table below); 3) the maximum point dose at least 2 cm outside the PTTV edge in any direction must be less than "D_{2cm}" (see column four in table below); and 4) the percentage of total lung volume receiving 20Gy or more (V20) should be less than 10% (see column five in table below).

Maximum PTV Dimension (cm)	Ratio of Prescription Isodose Volume to the PTV		Ratio of 30 Gy Isodose Volume to the PTV, $R_{30\ Gy}$		Maximum Dose 2 cm from PTV in any Direction, D_{2cm} (Gy)		Percent of Lung receiving 20 Gy total or more, V_{20} (%)		PTV Volume (cc)
	Deviation		Deviation		Deviation		Deviation		
	none	minor	none	minor	none	minor	none	minor	
2.0	<1.2	1.2-1.4	<3.9	3.9-4.1	<28.1	28.1-30.1	<10	0-15	1.8
2.5	<1.2	1.2-1.4	<3.9	3.9-4.1	<28.1	28.1-30.1	<10	10-15	3.8
3.0	<1.2	1.2-1.4	<3.9	3.9-4.1	<28.1	28.1-30.1	<10	10-15	7.4
3.5	<1.2	1.2-1.4	<3.9	3.9-4.1	<28.1	28.1-30.1	<10	10-15	13.2
4.0	<1.2	1.2-1.4	<3.8	3.8-4.0	<30.4	30.4-32.4	<10	10-15	21.9
4.5	<1.2	1.2-1.4	<3.7	3.7-3.9	<32.7	32.7-34.7	<10	10-15	33.8
5.0	<1.2	1.2-1.4	<3.6	3.6-3.8	<35.1	35.1-37.1	<10	10-15	49.6
5.5	<1.2	1.2-1.4	<3.5	3.5-3.7	<37.4	37.4-41.7	<10	10-15	69.9
6.0	<1.2	1.2-1.4	<3.3	3.3-3.5	<39.7	39.7-41.7	<10	10-15	95.1
6.5	<1.2	1.2-1.4	<3.1	3.1-3.3	<42.0	42.0-44.0	<10	10-15	125.8
7.0	<1.2	1.2-1.4	<2.9	2.9-3.1	<44.3	44.3-46.3	<10	10-15	162.6

11.0 Potential Adverse Reactions:

The adverse effects associated with the use of the Calypso transponder beacons are similar in profile to other bronchoscopic procedures such as bronchoscopic biopsies or the implantation of inert gold seed fiducial markers.

Pneumothorax: The most commonly encountered adverse effect of fiducial marker placement is pneumothorax which has a risk of between 2 to 5 percent[27,28] with the majority of these treated either conservatively or with a pigtail catheter for a day or two[24] after the procedure.

COPD Exacerbations: Exacerbations of emphysema or chronic obstructive pulmonary disorder (COPD) have been reported with a risk of up to 11 percent [29] in one small case series of 9 patients who had non-calypso beacons implanted. However, several much larger case series reported no COPD exacerbations[24,27,28] whatsoever.

Beacon Migration: Beacon migration has been reported at a rate of 1%[24] using anchored calypso beacons which can lead to the expectoration of the migrated beacon.

Infection: There is a 1% risk of pulmonary infection in the tissue in close proximity to an anchored Calypso beacon[24].

Minor Bleeding: There is a small risk of minor local bleeding in the airway implanted with the transponder beacon with a risk similar to other bronchoscopic based procedures, however no pulmonary hemorrhages were reported in the case series using the anchored Calypso lung beacon[24].

MRI compatibility: Anchored Calypso beacons can be safely scanned using MRI with either a 1.5 or 3.0 Tesla static magnetic field with or a magnetic field gradient of up to 9.3 Tesla/meter without inducing any clinically significant displacement force or torque. An MRI image artifact may extend up to 2 cm from the anchored transponder, which is of no clinical significance for patients on this trial since, outside of research studies, MRI is not used in the routine diagnosis of intrapulmonary lesions.

Retrieval of Calypso Beacons:
If an unanticipated adverse effect occurs with a Calypso beacon and removal of the beacon is required, then the anchored beacons can be retrieved using a flexible bronchoscope and forceps similar to other endobronchial foreign body retrievals.

12. 0 Evaluation During and After Protocol Treatment

	Baseline	4DCT Sim*	Each SABR Fractionφ	2 mo#	6 mo	12 mo	18 mo	2 yr	3 yr
History & Physical Exam	x			x	x	x	x	x	x
CT or MRI Brain	x								
CT Chest & Abdomen	x				x	x	x	x	x
PET Scan	x								
Chest X-ray				x					
Pulmonary	x				x		x		x

Function Testing									
6 min walking test	**x**				**x**		**x**		**x**
Medication Profile	**x**			**x**	**x**	**x**	**x**	**x**	**x**
CBC, Lytes, Bun, Cr	**x**								
EORTC QLQ - LC13	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Toxicity Profile (CTCAE V 4.0)	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Inter-beacon distance		**x**	**x**						

Notes:

*** 4DCT is to be performed no later than 4 calendar weeks after the date of beacon implantation**

φ The first fraction of SABR is to start no later than 14 calendar days after the 4DCT simulation scan

 # the timing of all follow up evaluations are relative to the date of the last fraction of SABR.

13.0 Statistical Considerations:

Descriptive characteristics:

Baseline patient, tumor, and treatment characteristics will be summarized using standard descriptive statistics as summarized in the table below.

Patient Factors	
Age	Mean & Standard Deviation
Gender	Percentage
Comorbidity (Charlson Index)	Mean & Standard Deviation
Smoking History Category (Current smoker, previous smoker, never smoker)	Percentage
Smoking Pack-Year History	Mean & Standard Deviation
FEV1 (Liters)	Mean & Standard Deviation
Diffusion Capacity (%)	Mean & Standard Deviation
6 Minute Walk Test (% of expected distance)	Mean & Standard Deviation
Tumor Factors	
T-stage (T1, T2)	Percentage
Tumor size (cm^3)	Mean & Standard Deviation
Tumor location (by lobe)	Percentage
Tumor Histology	Percentage
Treatment Factors	
GTV (cm^3)	Mean & Standard Deviation
PTV (cm^3)	Mean & Standard Deviation
Maximal observer tumor motion (cm)	Mean & Standard Deviation
Radiotherapy Dose Prescription (cGy)	Percentage
Radiotherapy Delivery Time Per Fraction	Mean & Standard Deviation

Study Power:
Power calculations were conducted using the STATA 12.0 statistical software package (College station, Texas). Zhao *et al.*[22] carried out dosimetric analyses of lung tumors undergoing SABR lung treatments with similar characteristics (T1-T2N0 NSCLC) to those which would be eligible for this study and found a median PTV volume of 62.9 cm^3 (sd 43.6 cm^3). Presuming similar sized tumor volumes as Zhao *et al.*, A sample size of 28 patients would yield a power of 0.92 to detect a 40% reduction in the mean PTV volume between standard ITV based SABR treatment as compared to gated calypso guided SABR, with an alpha value of 0.05 and using a 1-sided test for statistical significance.

Endpoints:

Percentage Change in PTV: For each participating patient, the PTV volumes will be calculated on the same 4DCT for standard ITV-based SABR treatment as well as the Calypso guided SABR treatment. The comparison of the PTV volumes will be calculated as follows:

$$\% \text{ change in PTV} = (PTV_{\text{standard SABR}} - PTV_{\text{Calypso Guided SABR}})/ (PTV_{\text{standard SABR}}) \times 100$$

This metric will be reported as a mean for the cohort with SD

Quality of Life Data: The mean EORTC QLQ – LC13 plus standard deviation will be tabulated in descriptive format for each evaluation time point.

Acute and Late Toxicity: The maximum grade of observed toxicity during treatment and follow-up will be tabulated in a descriptive format by adverse effect.

Percentage Change in Organ at Risk Dose Volume Metrics: For each organ at risk, percentage change in the dose-volume histogram metric of interest will be calculated as per the following example:

$$\% \text{ Change in Lung V20} = (V20_{\text{standard SABR}} - V20_{\text{Calypso Guided SABR}})/ V20_{\text{standard SABR}} \times 100$$

Pulmonary Function Test Results: Percentage change in pulmonary function test results (FEV1, DLCO, and 6 minute walk distance) will be calculated as per the following example at each follow-up time point:

$$\% \text{ Change FEV1} = (FEV1_{\text{baseline}} - FEV_{\text{follow-up}})/FEV1_{\text{baseline}} \times 100\%$$

Local Control: The RECIST[30] version 1.1 criteria will be used to assess the effect of SABR treatment on the local control of the tumor as per the following definitions:

RECIST Outcome	Description
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions taking as reference the smallest sum LD recorded since the treatment started or

	the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

7) Survival: Progression-Free Survival (PFS), Cancer-Specific Survival (CSS), and Overall Survival (OS) will be estimated using the Kaplan-Meier method. For all three survival estimates, the survival period will be defined as the time from tissue diagnosis to progression event (for PFS), Cancer related death (CSS), death from any cause (OS) or time of censoring (due to loss to follow-up, or end of study).

14. 0 Biobanking of Serum & Urine

In parallel to this study, patients will be offered voluntary participation in the Manitoba Tumor Bank (operating under auspices of the Manitoba Tumor Bank's Informed Consent Form). Blood and urine specimens from consenting volunteers will be collected at baseline, on the last day of SABR, at 6 months, and 1 year of follow up. This will allow for correlative biomarker studies to be performed in the future.

15.0 Ethical Considerations

This study will be carried out with the written approval of the biomedical research ethics board of the University of Manitoba. All patient care for this study will be in accordance with the principles of human medical research outline in the Declaration of Helsinki as adopted by the World Medical Association.

This study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirements. The investigators will be familiar with the appropriate study treatments as described in the protocol. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected.

16.0 Protocol Treatment Discontinuation

Patients may discontinue protocol treatment in the following circumstances:
1) Unacceptable toxicity (defined as any grade 3 or higher NCI CTCAE 4.0 acute toxicity relating to either the radiotherapy or the study drug); or
2) The development of an intercurrent illness that would preclude the continuation of the study treatment; or
3) Development of an intercurrent illness that would preclude further clinical assessments; or;
4) Request by the patient; or
5) Completion of study therapy and follow-up as per section 12; or
6) Cancer Cancer recurrence or progression (based on any combination of imaging, biochemical or clinical findings).

Patient management following stoppage of protocol treatment is to be reviewed by the Principal Investigators of the study (Dr. Julian Kim and Dr. Gordon Buduhan). This will allow the Principal Investigators to provide recommendations on the schedule and duration of additional follow-up, depending on the value of additional follow-up, patient convenience, trial safety, etc.

17.0 Serious Adverse Event Reporting

A serious adverse event (SAE) is any adverse event, regardless of causality that:

- Results in death.
- Is life-threatening. (When a patient is at immediate risk of death from a reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation. Hospitalisation admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Clarification should be made between the terms "serious" and "severe" since they are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious" which is based on patient/event outcome or action criteria described above and are usually associated with events that pose a threat to a patient's life or functioning. A severe adverse event does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria.

Serious Adverse Event requires reporting with completion of the SAE report. Fax the SAE report within 24 hours of the investigator knowledge or designee knowledge of the event to the attention of: Dr. Julian Kim and Dr. Gordon Buduhan to (204) 786-0194 (fax). Accrual may be stopped immediately as indicated upon review and confirmation of the SAE by the co-PIs in liaison with the investigator/ Research Ethics Board. This trial will conform to the monitoring requirements of Biomedical Research Ethics Board of the University of Manitoba.

18.0 Data Safety & Monitoring Committee

A committee consisting of non-trial related University of Manitoba affiliated personnel will serve as the Data Safety & Monitoring Committee. The committee will be chaired by a radiation oncologist (Dr. Andrew Cooke). Committee members will include a medical physicist (Dr. Anita Berndt), and a thoracic surgeon (Dr. Helmut Unruh). The DSMC will be convened after the fourteenth patient completes their first follow up visit after completion of their protocol mandated SABR treatments. Primary and secondary endpoints will be assessed. Should evidence of statistically significant detrimental effects of

the study intervention become apparent for the study's primary endpoints then futility will be declared and the trial will be closed.

19.0 Publication & Authorship

The results of this study will be prepared for publication in relevant peer-reviewed journals of radiation oncology/medical physics/thoracic oncology. It is anticipated that more than one publication will arise from this study. For clinical papers, the Co-Principal Investigators (JK, GB) will alternate first and senior authorship. All remaining co-investigators will be listed in descending order of their contributions to the overall success of the trial. Contributions to the success of the trial include but are not limited to: protocol design, drafting of grant applications, calypso physics commissioning/quality assurance, accrual of patients to the study, analysis of study results, and writing/editing of the manuscript. For physics based papers, a medical physicist will serve as a first author and a radiation oncologist (JK) will serve as the senior author. Co-investigators will 30 days from the receipt of manuscript drafts to return revisions or comments prior to submission for publication.

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APPENDIX I – EORTC QLQ - LC13 Quality of Life Questionnaire (Lung Cancer)

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

APPENDIX II – Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 - Respiratory Disorders

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Adult respiratory distress syndrome	-	-	Present with radiologic findings; intubation not indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by progressive and life-threatening pulmonary distress in the absence of an underlying pulmonary condition, usually following major trauma or surgery.					
Allergic rhinitis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an inflammation of the nasal mucous membranes caused by an IgE-mediated response to external allergens. The inflammation may also involve the mucous membranes of the sinuses, eyes, middle ear, and pharynx. Symptoms include sneezing, nasal congestion, rhinorrhea and itching.					
Apnea	-	-	Present; medical intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by cessation of breathing.					
Aspiration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Altered eating habits; coughing or choking episodes after eating or swallowing; medical intervention indicated (e.g., suction or oxygen)	Dyspnea and pneumonia symptoms (e.g., aspiration pneumonia); hospitalization indicated; unable to aliment orally	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by inhalation of solids or liquids into the lungs.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Atelectasis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., dyspnea, cough); medical intervention indicated (e.g., chest physiotherapy, suctioning); bronchoscopic suctioning	Oxygen indicated; hospitalization or elective operative intervention indicated (e.g., stent, laser)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by the collapse of part or the entire lung.					
Bronchial fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
Definition: A disorder characterized by an abnormal communication between the bronchus and another organ or anatomic site.					
Bronchial obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., mild wheezing); endoscopic evaluation indicated; radiographic evidence of atelectasis/lobar collapse; medical management indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by blockage of a bronchus passage, most often by bronchial secretions and exudates.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Bronchial stricture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., rhonchi or wheezing) but without respiratory distress; medical intervention indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by a narrowing of the bronchial tube.					
Bronchopleural fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
Definition: A disorder characterized by an abnormal communication between a bronchus and the pleural cavity.					
Bronchopulmonary hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the bronchial wall and/or lung parenchyma.					
Bronchospasm	Mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Limiting self care ADL; oxygen saturation decreased	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by a sudden contraction of the smooth muscles of the bronchial wall.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Chylothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thoracentesis or tube drainage indicated	Severe symptoms; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by milky pleural effusion (abnormal collection of fluid) resulting from accumulation of lymph fluid in the pleural cavity.					
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound.					
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an uncomfortable sensation of difficulty breathing.					
Epistaxis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated (e.g., nasal packing, cauterization; topical vasoconstrictors)	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the nose.					
Hiccups	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; interfering with sleep; limiting self care ADL	-	-
Definition: A disorder characterized by repeated gulp sounds that result from an involuntary opening and closing of the glottis. This is attributed to a spasm of the diaphragm.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Hoarseness	Mild or intermittent voice change; fully understandable; self-resolves	Moderate or persistent voice changes; may require occasional repetition but understandable on telephone; medical evaluation indicated	Severe voice changes including predominantly whispered speech	-	-
Definition: A disorder characterized by harsh and raspy voice arising from or spreading to the larynx.					
Hypoxia	-	Decreased oxygen saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO2 <=55 mm Hg)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a decrease in the level of oxygen in the body.					
Laryngeal edema	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., dexamethasone, epinephrine, antihistamines)	Stridor; respiratory distress; hospitalization indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the larynx.					
Laryngeal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies)	Death
Definition: A disorder characterized by an abnormal communication between the larynx and another organ or anatomic site.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Laryngeal hemorrhage	Mild cough or trace hemoptysis; laryngoscopic findings	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by bleeding from the larynx.					
Laryngeal inflammation	Mild sore throat; raspy voice	Moderate sore throat; analgesics indicated	Severe throat pain; endoscopic intervention indicated	-	-
Definition: A disorder characterized by an inflammation involving the larynx.					
Laryngeal mucositis	Endoscopic findings only; mild discomfort with normal intake	Moderate discomfort; altered oral intake	Severe pain; severely altered eating/swallowing; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by an inflammation involving the mucous membrane of the larynx.					
Laryngeal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the laryngeal airway.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Laryngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a narrowing of the laryngeal airway.					
Laryngopharyngeal dysesthesia	Mild symptoms; no anxiety; intervention not indicated	Moderate symptoms; mild anxiety, but no dyspnea; short duration of observation and or anxiolytic indicated; limiting instrumental ADL	Severe symptoms; dyspnea and swallowing difficulty; limiting self care ADL	Life-threatening consequences	Death
Definition: A disorder characterized by an uncomfortable persistent sensation in the area of the laryngopharynx.					
Laryngospasm	-	Transient episode; intervention not indicated	Recurrent episodes; noninvasive intervention indicated (e.g., breathing technique, pressure point massage)	Persistent or severe episodes associated with syncope; urgent intervention indicated (e.g., fiberoptic laryngoscopy, intubation, botox injection)	Death
Definition: A disorder characterized by paroxysmal spasmodic muscular contraction of the vocal cords.					
Mediastinal hemorrhage	Radiologic evidence only; minimal symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by bleeding from the mediastinum.					
Nasal congestion	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Associated with bloody nasal discharge or epistaxis	-	-
Definition: A disorder characterized by obstruction of the nasal passage due to mucosal edema.					
Pharyngeal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the pharynx and another organ or anatomic site.					
Pharyngeal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pharynx.					
Pharyngeal mucositis	Endoscopic findings only; minimal symptoms with normal oral intake; mild pain but analgesics not indicated	Moderate pain and analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; unable to adequately aliment or hydrate orally; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammation involving the mucous membrane of the pharynx.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Pharyngeal necrosis	-	-	Inability to aliment adequately by GI tract; tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the pharynx.					
Pharyngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a narrowing of the pharyngeal airway.					
Pharyngolaryngeal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pharyngolaryngeal region.					
Pleural effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., diuretics or limited therapeutic thoracentesis)	Symptomatic with respiratory distress and hypoxia; surgical intervention including chest tube or pleurodesis indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by an increase in amounts of fluid within the pleural cavity. Symptoms include shortness of breath, cough and marked chest discomfort.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Pleural hemorrhage	Asymptomatic; mild hemorrhage confirmed by thoracentesis	Symptomatic or associated with pneumothorax; chest tube drainage indicated	>1000 ml of blood evacuated; persistent bleeding (150-200 ml/hr for 2 - 4 hr); persistent transfusion indicated; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pleural cavity.					
Pleuritic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pleura.					
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.					
Pneumothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., tube placement without sclerosis)	Sclerosis and/or operative intervention indicated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormal presence of air in the pleural cavity resulting in the collapse of the lung.					
Postnasal drip	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by excessive mucous secretion in the back of the nasal cavity or throat, causing sore throat and/or coughing.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Productive cough	Occasional/minimal production of sputum with cough	Moderate sputum production; limiting instrumental ADL	Persistent or copious production of sputum; limiting self care ADL	-	-
Definition: A disorder characterized by expectorated secretions upon coughing.					
Pulmonary edema	Radiologic findings only; minimal dyspnea on exertion	Moderate dyspnea on exertion; medical intervention indicated; limiting instrumental ADL	Severe dyspnea or dyspnea at rest; oxygen indicated; limiting self care ADL	Life-threatening respiratory compromise; urgent intervention or intubation with ventilatory support indicated	Death
Definition: A disorder characterized by accumulation of fluid in the lung tissues that causes a disturbance of the gas exchange that may lead to respiratory failure.					
Pulmonary fibrosis	Mild hypoxemia; radiologic pulmonary fibrosis <25% of lung volume	Moderate hypoxemia; evidence of pulmonary hypertension; radiographic pulmonary fibrosis 25 - 50%	Severe hypoxemia; evidence of right-sided heart failure; radiographic pulmonary fibrosis >50 - 75%	Life-threatening consequences (e.g., hemodynamic/pulmonary complications); intubation with ventilatory support indicated; radiographic pulmonary fibrosis >75% with severe honeycombing	Death
Definition: A disorder characterized by the replacement of the lung tissue by connective tissue, leading to progressive dyspnea, respiratory failure or right heart failure.					
Pulmonary fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Limiting self care ADL; endoscopic stenting or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the lung and another organ or anatomic site.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Pulmonary hypertension	Minimal dyspnea; findings on physical exam or other evaluation	Moderate dyspnea, cough; requiring evaluation by cardiac catheterization and medical intervention	Severe symptoms, associated with hypoxemia, right heart failure; oxygen indicated	Life-threatening airway consequences; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by an increase in pressure within the pulmonary circulation due to lung or heart disorder.					
Respiratory failure	-	-	-	Life-threatening consequences; urgent intervention, intubation, or ventilatory support indicated	Death
Definition: A disorder characterized by impaired gas exchange by the respiratory system resulting in hypoxemia and a decrease in oxygenation of the tissues that may be associated with an increase in arterial levels of carbon dioxide.					
Retinoic acid syndrome	Fluid retention; <3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Moderate signs or symptoms; steroids indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; ventilatory support indicated	Death
Definition: A disorder characterized by weight gain, dyspnea, pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-trans retinoic acid.					
Sinus disorder	Asymptomatic mucosal crusting; blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow; limiting instrumental ADL	Stenosis with significant nasal obstruction; limiting self care ADL	Necrosis of soft tissue or bone; urgent operative intervention indicated	Death
Definition: A disorder characterized by involvement of the paranasal sinuses.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Sleep apnea	Snoring and nocturnal sleep arousal without apneic periods	Moderate apnea and oxygen desaturation; excessive daytime sleepiness; medical evaluation indicated; limiting instrumental ADL	Oxygen desaturation; associated with hypertension; medical intervention indicated; limiting self care ADL	Cardiovascular or neuropsychiatric symptoms; urgent operative intervention indicated	Death
Definition: A disorder characterized by cessation of breathing for short periods during sleep.					
Sneezing	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by the involuntary expulsion of air from the nose.					
Sore throat	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL; limiting ability to swallow	-	-
Definition: A disorder characterized by of marked discomfort in the throat					
Stridor	-	-	Respiratory distress limiting self care ADL; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a high pitched breathing sound due to laryngeal or upper airway obstruction.					
Tracheal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies)	Death

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by an abnormal communication between the trachea and another organ or anatomic site.					
Tracheal mucositis	Endoscopic findings only; minimal hemoptysis, pain, or respiratory symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammation involving the mucous membrane of the trachea.					
Tracheal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Stridor or respiratory distress limiting self care ADL; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a narrowing of the trachea.					
Voice alteration	Mild or intermittent change from normal voice	Moderate or persistent change from normal voice; still understandable	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; may require assistive technology	-	-
Definition: A disorder characterized by a change in the sound and/or speed of the voice.					
Wheezing	Detectable airway noise with minimal symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe respiratory symptoms limiting self care ADL; oxygen therapy or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by a high-pitched, whistling sound during breathing. It results from the narrowing or obstruction of the respiratory airways.					
Respiratory, thoracic and mediastinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death