MSK Protocol Cover Sheet

Calypso-based Deep Inspiration Breath Hold (DIBH) Radiation Treatments of Lung Cancer

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This trial will investigate the feasibility of implanted anchored Beacon® electromagnetic lung transponders (Calypso®) to guide and monitor deep-inspiration breathhold (0IBH) treatments in patients with inoperable thoracic malignancies. Currently, many patients with thoracic tumors cannot be treated to the optimal intended radiation dose due to strict dosimetric limitations for normal tissues nearby. Furthermore, all lung tumors that are treated to the full radiation dose exhibit tumor motion with respiration which requires the radiation field to be expanded to an internal target volume (ITV) that encompasses all possible tumor positions during the treatment in order to avoid missing the target. This results in the unnecessary treatment of larger amounts of normal lungs, esophagus and other nearby organs at risk which are responsible for the majority of adverse events in thoracic radiation oncology.

Several techniques to reduce respiratory motion during radiation therapy have been explored and are clinically available. One of the most promising approaches is to immobilize the tumor by having patients hold their breath. This has been found to result in effective reduction of tumor motion as well as an expansion of the lungs and other normal tissues to be moved away from the radiation target. However, 0IBH is currently performed based on external markers and radiographic surrogates such as the diaphragm to monitor the patient's breathhold. It is known that external markers and the diaphragm frequently do not correlate well with internal motion and tumor position. Using implanted Calypso beacons would for the first time allow real-time monitoring of tumor position and breathhold in patients with thoracic malignancies. This technology was initially developed for prostate cancer patients with great success. A new anchored lung transponder has been developed for its application in thoracic malignancies in which there is significantly more tumor motion. Based on our experience in prostate cancer patients, it is our expectation that this transponder would improve the reproducibility of localizing and monitoring tumor position during breathhold in real time, decrease radiation dose to organs at risk in close proximity to the radiation target and allow dose escalation to desired radiation doses. In addition, limiting tumor motion to a minimum and thus increasing our confidence in intrafraction tumor position would allow decreasing the ITV margins that are currently added to the tumor to account for tumor motion. This would ultimately lead to improved local control rates and decreased adverse events attributable to the radiation treatments.

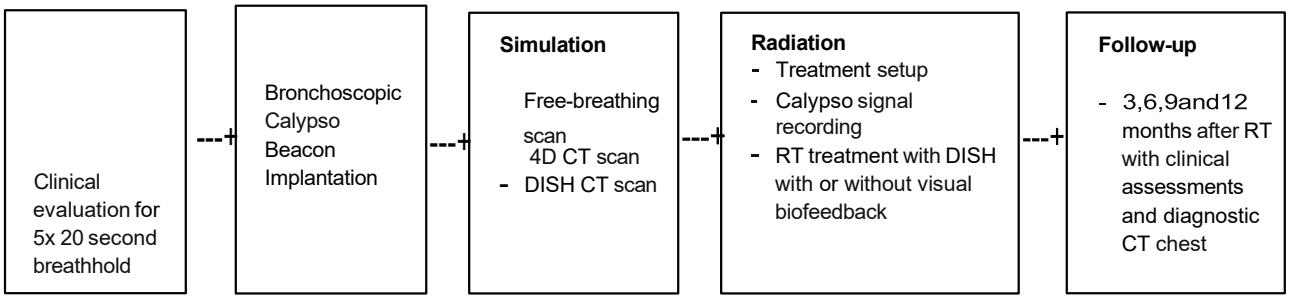
Patients who are able to hold their breath at least for 5 breathholds of more than 20 seconds each and are planned to undergo radiation treatment to tumors in the thorax will be eligible for this study.

First, 2-3 anchored lung transponders will be placed bronchoscopically in or near the target tumor. Patients will be given instructions to learn and practice the 0IBH maneuver. After a minimum of 3 days, the patient will undergo a CT simulation for radiation treatment planning, and a free-breathing 4D CT scan and a CT scan in 0IBH will be obtained using the Varian® Real-time Position Management™ (RPM) system. Two radiation therapy plans will be developed, one based on the free-breathing 4D CT scan and one based on the 0IBH scan. At the time of treatment, the patient will be initially positioned according to standard setup

procedures based on external tattoos and room lasers. A free- breathing trace of the Calypso transponders will be obtained to allow the patient to settle on the treatment table and to study real-time respiratory traces. The patient will then be asked to perform a therapist-coached modified slow vital capacity maneuver and DIBH maneuver [1] and hold their breath. Patients will have the ability to perform this maneuver with or without biofeedback from digital goggles that are placed over the patient's eyes and display the breathing trace of the Calypso transponders. The use of the digital goggles will be determined by patient preference or at the discretion of the treatment team. This will allow us to investigate whether real-time biofeedback adds to the reproducibility of patients holding their breath. A DIBH cone-beam CT will be acquired in approximately three breath-holds, once a week for standard fractionated RT patients or with each fraction for SBRT patients. After review and approval of the images, the patient will be treated while holding their breath using the DIBH maneuver. In standard fractionated RT patients the radiation treatment will be guided by the external tattoos and daily 2D kV imaging. The Calypso transponder signal will be used to monitor the level of the breath-hold during treatment. The breath-hold level based on the Calypso transponder signal will be verified daily by the 2D imaging and once a week in 3D by the DIBH cone-beam CT. In SBRT patients, the radiation treatment will be guided by the external tattoos and daily DIBH cone-beam CT. The Calypso transponder signal will be used to monitor the level of the breath-hold during treatment. The therapists will monitor the respiratory trace signal from the Calypso transponders throughout the treatment and will initiate the radiation treatment delivery when the patient holds his/her breath within the tolerance level the patient has been assigned to. This will be continued up until the initially planned 30 patients are accrued.. Should the transponder signal indicate that the target has moved outside of the preset tolerance, the therapists will hold further radiation treatment delivery until the patient's breathhold has returned to the desired target range or until the patient's setup has been corrected. In the additional 25 patients planned, the margins will be reduced in a step-wise fashion. The gate will be decreased 1mm per each set of 5 patients until the duty cycle (beam-on time) and number of DIBH attempts are doubled. The gate at which this occurs will be considered the minimum clinically feasible gate

The study will determine for the first time based on real-time tumor positioning information whether patients are able to reproducibly hold their breath in DIBH within excursions of 5.+/- 0.5cm or less. Furthermore, it will determine whether visual biofeedback improves the reproducibility of the breathhold. It will provide a unique dataset that will allow us to determine the concordance level of real-time tumor position information from the Calypso transponders, external surface signal and radiographic imaging. Ultimately, this study will allow us to quantify the decrease in radiation dose to organs at risk, decreased toxicity and amount of dose escalation made possible by the DIBH maneuver using real-time tumor position information.

Patients will be considered evaluable for protocol when they have had successful calypso beacon implantation without the beacons migrating> 5cm, and they have completed training in DIBH. In the extension of the protocol described below, 25 patients will be accrued; the expected time for completion of this study is 3 year from its approval.


Clinical evaluation for 5x 20 second breathhold
Bronchoscopic Calypso Beacon Implantation
Simulation
Free-breathing scan
4D CT scan
DISH CT scan
Radiation
Treatment setup
Calypso signal recording
RT treatment with DISH with or without visual biofeedback
Follow-up
3,6,9and12 months after RT with clinical assessments and diagnostic CT chest

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary objectives:

- To evaluate the feasibility of using internal tumor surrogates (Calypso beacons) during repeated deep inspiration breath hold maneuvers for DIBH radiation treatments.

Secondary objectives:

- To compare the reproducibility with visual versus without visual biofeedback.
- To assess differences in the ability of maintaining the DIBH maneuver within the gate with and without visual biofeedback
- To measure the residual intrafraction tumor motion and associated improvement in normal tissue dosimetry during DIBH based on the Calypso lung transponder signal as a surrogate
- To measure the increase in dose escalation and the potential for decreasing margins made possible by Calypso-guided DIBH
- To determine the minimum clinically feasible gate margin for radiation
- To assess tumor shrinkage, beacon position and centroid changes in conventionally fractionated patients
- To assess intra- and inter-fraction variation in lung volume preservation of multiple DIBH maneuvers

3.0 BACKGROUND AND RATIONALE

3.1 Respiratory motion in lung cancer radiation treatment

Non-small cell lung cancer (NSCLC) remains the malignancy associated with the highest number of cancer-related deaths in the US.

Patients with inoperable early-stage NSCLC are typically treated with high-dose stereotactic body radiation therapy (SBRT) resulting in excellent local control of >90%.[2-5] SBRT is now also being used for metastatic disease in the lungs, with equally good local control rates and low rates of toxicity as observed in early-stage NSCLC.[8-11] Currently, a 4D free breathing CT scan is obtained at simulation. The 4D scan is used to determine the entire volume swept out as the tumor moves through the respiratory cycle. This volume (the ITV) is further increased by the addition of 0.5 to 1 cm margins of healthy tissue to create the volume (the target) which is treated to the prescription dose. The margins of healthy lung are needed to account for positioning uncertainties during treatment. Significant respiratory tumor motion results in an increase of the ITV and therefore the volume of healthy lung within the target volume. The volume of healthy lung within the target, and the volumes of adjacent normal tissues such as chest wall increase rapidly with increasing ITV size. Since these patients are usually medically inoperable due to severe emphysema or other medical comorbidities, any reduction in radiation dose to organs at risk is desirable. The most common toxicities observed with SBRT include respiratory toxicity, esophagitis, chest wall pain, and rib fractures. The rate of toxicities from SBRT appears to be directly related to the irradiated volume, the tumor

location and the radiation dose.[5-7]

Locally-advanced NSCLC patients receive fractionated RT, ideally 60 Gy in 30 fractions when given with concurrent chemotherapy.[12-14] Frequently, the predicted toxicity from radiation dose to the lungs and spinal cord using widely agreed upon dose constraints to these organs limit our ability to treat patients to the optimal prescription dose. [15, 16] Respiratory motion can significantly increase the treated volume, especially in patients with already large tumors. The most common toxicities in this patient population are esophagitis and respiratory toxicity including radiation pneumonitis.[14, 17] The same challenges exist for patients with limited-stage small cell lung cancer treated with chemotherapy and thoracic radiation therapy.[18-20] Techniques to address intrafraction tumor motion include abdominal compression, respiratory gating, and active breathing control (ABC).[21] While these are all clinically approved techniques, they are not currently widely used in practice. Abdominal compression can be uncomfortable to the patients and does not necessarily control internal motion well.[22] In addition, it compresses the lungs and does not consistently improve sparing of normal tissues, but may actually worsen the dosimetry.[23] Respiratory gating based on external markers can be misleading due to the potential discrepancy between external marker and true internal target motion.[24, 25] ABC is an involved process using a spirometer which is frequently uncomfortable to the patient, and there are problems with changes in tidal volume, volume expansion, patients' response and adaptation to the system.[26, 27] These techniques all depend on unreliable surrogates of the target position, and frequently cannot be tolerated by patients because of patient discomfort or are too complex for patients to manage, making them far from ideal .

In principle, DISH is a promising approach to minimize respiratory motion. It has been shown to reduce respiratory motion, increase lung volume, and allow dose escalation.[1, 21, 28, 29] Currently, DISH is feasible in about 25% of patients who undergo lung radiation therapy. This is because of the difficulty many patients have in adequately performing the modified slow vital capacity maneuver currently used for DISH, which consists of a deep inhalation, deep exhalation, second deep inhalation and breath hold. When performed well, the maneuver results in a reproducible lung inflation and thereby tumor position. We currently use it in selected patients who are able to perform this maneuver well. Currently, DISH is based on external markers e.g. RPM, or radiographic surrogates such as the diaphragm, since lung tumors are typically not well enough delineated on 2D radiographs. However, DISH based on surrogates like external markers and radiographic surrogates such as the diaphragm is fraught with the same problems as respiratory gating based on external markers or the ABC device. There may be a lack of correlation between external marker and internal target motion, e.g. drifts or shifts of the internal target that may not be accurately detected by an external marker.[24, 25]

We therefore propose using implanted Calypso lung transponders for guidance and monitoring of DISH in patients with thoracic malignancies who are treated with radiation therapy. This would represent a significant improvement over current DISH techniques

by having available reliable, real-time tumor position information prior to and throughout the radiation treatment delivery. With real-time tumor position feedback, it will not be necessary to perform the difficult DIBH maneuver; instead, a simple inhalation and breath hold will be sufficient to position the tumor with high reproducibility. We expect this to substantially improve the patient eligibility rate compared to other methods for DIBH guidance, such as spirometry or external markers. As a result, we expect to more frequently be able to treat patients with locally-advanced lung cancers to the intended total dose of 60 Gy as a direct benefit to patients from using this technique. If successful this study will lead to a new clinical technique that will allow us to decrease the volume of healthy lung and adjacent tissues exposed to high doses, thus further decreasing the risk for toxicities. This makes possible a strategy for dose escalation and thus the potential for improved local control in patients where current treatments are limited by normal tissue constraints.

3.1.1 Rationale for the use of Calypso lung transponders

In prostate cancer RT, the use of electromagnetic Calypso transponders has been found to allow real-time tracking of inter- and intrafraction motion, as well as reduction in PTV margins and patient-reported acute morbidity.[31-33] Submillimeter accuracy was established to a range of 27cm distance from the detection array and at speeds of up to 3cm/s, thus making it the most accurate real-time motion monitoring device available.[34] Electromagnetic Calypso transponders revealed prostate motion of >5mm in 97% of patients, thus providing a significant benefit over conventional patient positioning. In addition, a cost-utility analysis demonstrated significant benefits in quality-adjusted life years (QALY) compared to conventional localization.[35] Outside of prostate cancer, these transponders have been shown to also be feasible for inter-and intrafraction motion detection in pancreatic cancer.[36] The implantation of the transponders as part of the staging laparoscopy was well-tolerated and minimal migration of the transponders was observed. It was shown that breathholding significantly decreased tumor motion.

Until recently, no such transponder system was available for lung tumors, due to the difficulty of developing a transponder that would stay fixed after implantation. Varian Medical has now developed a modified transponder for use in lung cancer by adding anchors to the same transponders that are in routine clinical use for prostate cancer. The anchors of the lung transponder stabilize the transponder in small airways of the lungs. A pilot study from the University of Stellenbosch, Tygerberg, South Africa, and the University Hospital Basel, Basel, Switzerland, has found the first use in humans to be safe and feasible.[22, 37] No patients developed pneumonia, pneumothorax or adverse pulmonary symptoms. Significant intrafraction variability of tumor motion was detected, even with the use of external compression devices. Currently, these anchored transponders are being tested for safety and feasibility in the lungs in an ongoing larger clinical study ("Evaluating an Anchored Transponder in Lung Cancer Patients Receiving Radiation Therapy" (NCT01396551), www.clinicaltrials.gov). Preliminary findings of this study in the US showed that out of 48

evaluable patients, two patients experienced a pneumothorax (Grade 2), one patient had anesthesia-related cardiac arrest (Grade 4), two patients experienced cough (Grade 2) and one patient had dyspnea (Grade 2) after the bronchoscopy, one patient had lung infection (Grade 3), and two patients had migration of one fiducial marker each that did not impact the ability to track the tumor during radiation treatments.[38, 51.] The use of Calypso transponders holds the potential for a great benefit of real-time tumor position information without the use of ionizing radiation from additional intrafraction imaging. Calypso transponders have been routinely used in our department as a motion monitoring system for prostate RT for about 5 years. The entire system including 4D console, electromagnetic array, tracking station and optical system is in place on a linear accelerator that is equipped for lung RT and on-board kV imaging.

3.1.2 Rationale for the use of SuperDimension® system and radial probe Endobronchial Ultrasound

The SuperDimension® system is an electromagnetic navigation bronchoscopy (ENB) system that allows minimally invasive procedures in the periphery of the lungs with higher accuracy than conventional bronchoscopy alone[39]. It allows bronchoscopic biopsies, fine needle aspirations and fiducial marker placements with a reduced risk of pneumothorax as compared to transthoracic approaches. Given its extended range it has been shown to reach peripheral lung tumors with accuracy >80%. This system allows for virtual guidance based upon CT reconstructions and electromagnetic tracking. Therefore, real-time confirmation can be provided by radial probe endobronchial ultrasound (rEBUS; Olympus Medical) which further improves the accuracy.[40, 41] In certain cases, rEBUS alone is sufficient to localize peripheral pulmonary lesions.[42-45] However, it has been shown that the combination of these technologies provides the highest diagnostic yield for biopsies of peripheral lung lesions by improving lesion localization accuracy. Both of these localization technologies are in routine use by our interventional pulmonologists and thoracic surgeons and are fully compatible with the Calypso anchored transponder system.

Prior studies have demonstrated safety in placing other fiducial markers bronchoscopically (ENB +/- rEBUS) for lung tumors with low migration rates and low pneumothorax rates.[46-48] Comparisons of transcutaneous versus ENS-guided fiducial marker placement shows a higher risk of pneumothorax in the transcutaneous group.[48] Furthermore, early studies in Switzerland and South Africa have shown the feasibility, stability and safety of bronchoscopic Calypso transponder placement.[37] We therefore propose to use the SuperDimension ENB system and rEBUS for the placement of Calypso transponders whenever possible. Alternatively, conventional bronchoscopy may be used for Calypso transponder placement where feasible. Radial probe endobronchial ultrasound (EBUS) may be used when needed for more accurate placement of the Calypso transponders.

3.2 Preliminary Data

DIBH has been previously explored using coached breath-hold monitored by spirometry [28, 49] and radiographic imaging and using spirometry plus the Elekta "ABC device" together with radiographic imaging[21][18, 27]. An initial series of 5 patients at MSKCC who underwent CT scans under 4 different respiration conditions including DIBH showed that DIBH can reduce the volume of lung receiving more than 25 Gy by 30% compared to free-breathing radiation plans. Patients were able to comfortably hold their breath for 12 -16 seconds and perform 10-13 breath-holds in a single session.[28]

We then showed that coached DIBH with spirometer monitoring decreased estimated normal tissue complication probabilities while allowing for increased tumor doses.[1] Patients were initially maintained at quiet tidal breathing, followed by a deep inspiration, a deep expiration, a second deep inspiration, and breath-hold in deep inspiration (DIBH). Simulation, verification and radiation treatments took place during this last phase of DIBH. Seven patients received a total of 164 treatment sessions with excellent tolerability. None of the seven patients needed to discontinue treatment or resume the free-breathing backup method due to fatigue or inability to perform the DIBH maneuver. On average, the radiation dose could be increased from 69.4 Gy to 87.9 Gy without increasing the risk of toxicity by using DIBH.

In a subsequent analysis of 7 patients undergoing over 250 treatments, we found that reproducibility was excellent as judged by spirometry and verification films using the diaphragm as a surrogate. Presumed respiration-dependent tumor motion was thus significantly reduced from 0.8 +/- 0.5cm to 0.02 +/- 0.14 cm (mean and standard deviation) compared to free breathing.[49] The main advantages observed with the use of DIBH were an increase in lung volume and motion of the PTV away from critical structures, e.g. spine. Thus, DIBH is an excellent tool to decrease target motion, decrease radiation dose to normal organs at risk and thus allow dose escalation to the tumor. DIBH treatments are currently clinically used in our department in appropriate patients. However, all DIBH treatments to date have relied on external or indirect markers as surrogates, sometimes combined with fluoroscopy or radiographic imaging for position verification. Given the potential pitfalls of external surrogates, we propose to investigate and improve DIBH treatment delivery using real-time tumor position information from implanted electromagnetic Calypso anchored transponders. In addition, the use of Calypso anchored transponders would simplify the DIBH maneuver to a single, comfortable breathhold, thus making it an attractive treatment option for a wider patient population.

Early studies in Switzerland and South Africa have shown the feasibility, stability and safety of bronchoscopic Calypso anchored transponder placement.[37] They have also demonstrated successful intrafraction motion detection.[22] An ongoing prospective international trial explores the safety and feasibility of endobronchial implantation of these electromagnetic fiducials. Interim results reported at ASTRO 2012 showed that 149 transponders were successfully implanted in 48 patients.[38, 51.] Two patients developed cough (G2), 1 patient

had dyspnea (G2) after bronchoscopy, two patients had pneumothoraces (G2), one patient had an anesthesia-related cardiac arrest (G4), and one patient had a lung infection (G3) concurrent with marker migration. One other patient experienced an asymptomatic migration of one transponder in a large airway that did not prevent localization and tracking by the Calypso system. Positional stability of these transponders is therefore 99% to date.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

The primary objective of this study is to evaluate the feasibility of Calypso transponders as an internal tumor surrogate to guide DIBH radiation treatments in real time.

The use of Calypso transponders has the potential to result in improved reproducibility of tumor positioning during DIBH treatments. We therefore plan to analyze the obtained respiratory traces from the Calypso signal as well as the imaging data from CBCTs and radiographs to explore a set of secondary objectives. These include a comparison of the reproducibility of DIBH tumor position with visual versus without visual biofeedback (for patients who agree to use the digital goggles), measurement of any residual intrafraction tumor motion, improvement in normal tissue dosimetry during DIBH based on the Calypso lung transponder signal as a surrogate, and determination of any increase in dose escalation and the potential for decreasing margins made possible by Calypso-guided DIBH. Given the successful radiation localization in the first 25 patients, we will also aim to determine the minimum clinically feasible gate margin for radiation. We will reduce the gate from +/-5mm by 1mm for every 5 patients treated. Once the minimum gate is determined, the remaining patients will be treated at +1mm from this value. We will also plan to enroll at least 10 additional conventionally fractionated patients to assess the impact of tumor shrinkage on beacon position and centroid changes. Finally, lung volume preservation will be assessed on wide field of view cone-beam CTs and compared intra- and interfraction within each patient to check for reproducibility or variability of lung volumes across multiple DIBH maneuvers.

The radiation treatment for patients on this study will be performed according to routine procedures using standard equipment, techniques and treatment planning procedures. The radiation dose prescription criteria will not be changed based on the DIBH maneuver or Calypso transponder implantation on this study. Patients will be followed as per our institutional standard at approximately 3, 6, 9 and 12 months after radiation treatments. Following completion of study participation, patients will be followed as per our institutional standard. They will be evaluated for any potentially transponder-related toxicity. Any toxicities will be carefully evaluated case by case according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

4.2 Intervention

The Calypso signal will be used to verify and monitor the patient's DIBH maneuver at each treatment session. In addition, physician evaluation of patient setup accuracy will be performed using all available images and adjustments will be made as per standard practice. Should the transponder signal indicate that the target has moved outside of the preset tolerance, the system will automatically hold further radiation treatment delivery until the patient's breathhold has returned to the desired target range or until the patient's setup has been corrected.

For imaging, we will use the on-board kV imaging system. Patients undergoing SBRT will receive standard CBCTs for patient setup, but no more than 2 CBCTs per treatment for protocol purposes. Patients undergoing conventionally fractionated RT will undergo weekly imaging sessions with CBCT for protocol purposes. A maximum of 8 CBCTs over the entire treatment course will be permissible for protocol purposes in patients undergoing conventionally fractionated RT.

Radiation therapy dose guidelines, treatment planning process and followup will not be changed by enrollment on this study.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

The major components required for this study are the anchored Calypso beacon transponders, the SuperDimension electromagnetic navigation bronchoscopy system, Olympus radial probe endobronchial ultrasound and RPM system on the simulator and the Calypso tracking system at the treatment machine.

The anchored Calypso beacon transponders and training and user documentation will be provided by Varian Medical Systems, Palo Alto, CA, as part of a research agreement. The Calypso Anchored beacon transponders received FDA 510(k) clearance. Previously, a physician-sponsored investigational device exemption {IDE) application had been approved by the Food and Drug administration (FDA) to permit the use of Anchored Beacon Transponders in lung for this study. A cross-reference to the IDE for the ongoing Calypso feasibility trial which is already on file at the FDA has been kindly provided by Varian Medical Systems.

The SuperDimension ENB and Olympus rEBUS are both in routine use by our Interventional Pulmonology and Thoracic Surgery services including the disposable GuideSheath Extended Working Channels (EWC), Locatable Guides (LG), and the planning and navigation software.

Prior to undergoing treatment, the patient will have a CT chest for Navigation performed at MSKCC. The images obtained from this specially formatted CT scan will be uploaded into

the SuperDimension iLogic software suite. The lesion of interest will be selected, a 3-D airway model created and a pathway(s) to the lesion will be selected and confirmed. This "patient plan" will be brought to the operating room for use during the placement of the Calypso fiducials, as part of the standard use of the SuperDimension ENB system. The following is an outline of the basic schema of how the procedure will be performed:

Bronchoscopic Intervention with Calypso beacon transponder placement:

1. Pre-operative "patient plan" created and confirmed to be appropriate for beacon transponder placement
2. Anesthesia induction via laryngeal mask airway or endotracheal tube
3. Standard bronchoscopic evaluation of the airways
4. The LG and EWC are advanced through the working channel of the bronchoscope
5. Registration of the SuperDimension ENB system 3-D model with the airways in real time is performed
6. Navigation of the LG and EWC to the lesion of interest
7. Flouroscopy to confirm location of EWC and that it does not move during the placement of the beacon transponders
8. Removal of the LG while maintaining the EWC in place
9. Confirmation with rEBUS that the EWC is at the lesion of interest
10. Placement of 3 Calypso beacon transponders in or near the lesion of interest under fluoroscopic guidance
11. Fluoroscopic confirmation of placement
12. Removal of EWC
13. Final bronchoscopic evaluation of the airways
14. Emergence from anesthesia with standard post-procedural care, including a portable CXR

During the procedure, all care will be taken to reduce the risk of adverse events for the placement of the fiducials. The use of Olympus rEBUS and fluoroscopy, in addition to the SuperDimension ENB system, will further reduce the risk of adverse events, including pneumothorax. As previously noted, the risk of adverse events during the placement of fiducials is very low, with the majority of the risk associated with anesthesia. [37, 46-48, 50].

There is an inherent increased risk for these patients since they will have to undergo a bronchoscopy for the placement of fiducials as part of the radiation therapy, unlike patients who are undergoing radiation therapy without fiducial placement. Since the majority of these patients have many medical comorbidities and have been deemed non-operable, a complete pre-operative assessment will be performed by either the Thoracic Surgery or Pulmonology service, with standard anesthesia evaluation done during pre-surgical testing, to confirm that the patient is an acceptable risk for anesthesia. This may include formal cardiac and pulmonary studies, as well as appropriate specialty consultations, including internal

medicine, geriatrics or cardiology, at the discretion of the treating physician. If it is determined that the risk of anesthesia is too great, the patient will not be eligible for this study.

The entire Calypso monitoring system including 4D console, electromagnetic array, tracking station and optical system is in place and currently in routine use for prostate cancer patients. The linear accelerator is equipped for intensity modulated radiation therapy as is used for lung RT and on-board kV imaging. For patients who agree to use the digital goggles, the visual feedback of the Calypso signal will be captured by an iPhone that records the Calypso signal on the screen. This will be transmitted to a pair of video goggles or an iPhone to be viewed by the patient. The visual feedback system is not part of the Calypso device. We have successfully tested, on volunteers, the ability of this system to adequately display the signal on the viewing device.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Patients must have histologic proof of malignancy suitable for thoracic radiation therapy
- Patients planning to undergo radiation therapy for primary or recurrent malignancy of the lung or metastatic malignancy to the lung.

  Note: this may be delivered by SBRT or standard fractionation, based on the discretion of the treating physician.
- Age 18 years old
- KPS 60%
- Ability to hold their breath for >20 seconds for 5 times
- Patients who are able to tolerate flexible bronchoscopy
- Patients with life expectancy of at least 12 months
- Patients able to have bronchoscopic placement of Calypso transponders as confirmed on a recent (within the past 8 weeks) CT scan.
- Patients who are able to comply with the protocol follow-up schedule.

6.2 Subject Exclusion Criteria

- Patients unable to comply with instructions for DIBH
- Patients with implants in the chest region that contain metal or conductive materials (e.g., metal implants, rods, or plates) which Varian Medical considers will interfere with the Calypso System's electromagnetic localization.
- Patients with active implanted devices, such as pacemakers, defibrillators, and drug infusion pumps since the effects of the Calypso System operation on these devices are unknown.
- Patients with clinically significant active infections.
- Patients with bronchiectasis in the region of the intended implantation sites.

- Patients with a history of hypersensitivity to nickel.
- Patients whose lung tumors are being monitored with **MR** imaging **(MR** imaging of the anchored transponders is safe but yields an image artifact around the anchored transponders).
- Posterior lesions that would be >19cm distance from Calypso detector plate. Patients may be treated in the prone position in order to meet the required minimum distance.
- Patients with any other medical condition or laboratory value that would, at the discretion of the investigator, preclude the patient from participation in this clinical study.
- Patients who are deemed unable to safely undergo or tolerate flexible bronchoscopy
- Patients who are unable to tolerate anesthesia or sedation
- Patients enrolled in any other clinical studies the investigator believes to be in conflict with this investigation.
- Female patients who are pregnant or nursing

7.0 RECRUITMENT PLAN with Limited Waiver of Authorization

Patients will be evaluated by the attending physician from the Department of Radiation Oncology and entered onto the study if they are appropriate. The attending physician, or his designate, will obtain informed consent from the patient.

We have taken notice of NIH/ADAMHA policies concerning the inclusion of women and minorities in clinical research populations. We expect that the study population will be fully representative of the range of patients seen at MSKCC without exclusion to age (> 18 years), or ethnic background. Given the limited number of subjects to be entered onto the study, no specific outreach efforts are planned.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient

is eligible and to contact the patient regarding study enrollment. Patients will be asked to perform a DIBH maneuver in clinic of five breathholds of 20 seconds each. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

The initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reason, we seek a limited waiver of authorization for the purposes of (1) reviewing relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

We expect to accrue 1-2 patients per month for a total of 30 patients.

8.0 PRETREATMENT EVALUATION

- Pathology review to confirm diagnosis
- History and physical exam
- The DIBH maneuver consists of a comfortably deep inhalation followed by a breath hold. Patients will be clinically tested (typically at the time of consultation) to hold their breath for a minimum of 20 seconds xS times in a simulated treatment position with their arms raised above their heads. The patient will be asked to practice at home, and coaching will be repeated at the time of treatment.
- CT scan of the chest for navigation
- Pregnancy test, if applicable
- Consultation with thoracic surgery or interventional pulmonology for transponder implantation

9.0 TREATMENT/INTERVENTION PLAN

Using ENB and rEBUS, three Calypso transponders will be bronchoscopically placed within a small bronchial airway according to the Anchored Beacon Transponder Instructions for Use provided by Varian Medical (see section 20.0 Appendices). Two Calypso transponders will be permissible if it is technically not possible to place three transponders, as the tracking system works with a minimum of two transponders. Placement within 2 cm from the pleura should be avoided if possible to minimize the risk of pneumothorax. The position of the anchored transponders will be verified by fluoroscopy at the time of placement.

After a minimum of 3 days, the patient will be brought to the radiation simulation suite and immobilized using a custom-mademold, as per our standard protocol. Immobilization will be in a supine position unless prone treatment is required to meet the distance requirement

between the Calypso beacons and the Calypso detector plate. The patient will be coached through the DIBH maneuver and a breath-hold level that the patient can comfortably and reproducibly achieve using the Calypso system will be determined. A free-breathing (FB) 4D CT scan of the thorax and a CT scan in DIBH mode will be obtained using the RPM system. The patient's position and setup will be documented by tattoos and photographs.

Target volumes and normal structures will be delineated on the FB scan and on the DIBH scan. Target delineations will be performed on the registered 4DCT image set and on the DIBH scan as per current clinical practice. The Calypso beacons will also be delineated on each phase of the 4DCT study and on the DIBH scans.

Analysis of the 4DCT will provide an initial evaluation of the motion concordance between the Calypso beacon and the RPM external marker. Two radiation treatment plans will be developed, one based on the free-breathing scan and one based on the DIBH scan. These will be used for dosimetric comparison of treatment plans between a free-breathing and DIBH treatment. Only the DIBH treatment plan will be used clinically, unless a patient is unable to complete the DIBH maneuvers at the time of treatment. In that case, the plan based on the FB scan will serve as a backup plan. The beacon coordinates for the DIBH scan will be input to the Calypso system.

In the additional 25 patients to be accrued the window will be reduced in a step-wise fashion by 1mm for every 5 patients. Number of beam holds, treatment interruptions and total treatment time from first beam-on time to the last beam-off time will be recorded by the therapists.

If a patient cannot achieve the desired breath hold after 3 attempts and discussion with the therapist, the therapist can treat with the best breath-hold achievable and report the change in level to the treating physician. Additionally, the therapist will acquire an orthogonal pair of images. The physicist will then estimate the dosimetric effects per day in case the patient is still unable to achieve adequate breath hold the next day. Depending on the estimated dosimetry and the patient's reasons for not being able to achieve breath hold, the patient may be taken off protocol if unable to perform the breath hold to within +/- 5 mm for 3 consecutive treatment days. Patients who are taken off protocol prior to treatment completion will be treated based on the free-breathing treatment planning scan for the remainder of the radiation treatment course.

9.1 For patients undergoing SBRT in 10 or less fractions, the following procedures will be performed:

1. Standard setup procedures based on external tattoos will be performed.
2. The Calypso antenna will be deployed and positioned over the patient's chest. Tracking of the Calypso transponder signal will commence.

3. For patients who have been selected to use the digital goggles, the DIBH maneuver will be performed with visual biofeedback at least once a week and at least one fraction will be done without visual feedback. During treatment the radiation therapist will coach the patient on how to hold their breath during the treatment. On treatment days with visual feedback, the patient will be able to view and control his/her breathing through biofeedback using goggles (Myvu Personal Media Viewer, Myvu Corporation) or an iPhone that displays the Calypso trace. The couch position will be adjusted by the therapists in the treatment room to accurately set up the patient for treatment in DIBH based on the Calypso signal. The Calypso trace will be set to zero based on the DIBH level.

4. The patient will resume regular breathing and the therapists will leave the room.

5. The patient will be remotely asked to repeat the DIBH maneuver and a CBCT will be obtained over several breathholds (exact number depending on the patient's ability to hold their breath) using partial arcs and the assigned breath hold tolerance window.

6. The CBCT images will be evaluated and the patient will be repositioned for a soft tissue match as needed. The soft tissue match will then be evaluated and approved by the treating physician as is our normal clinical process. The isocenter coordinates in Calypso will be changed based on the patient's repositioning shift dictated by the CBCT soft tissue match. No more than 2 CBCTs per treatment will be done for protocol purposes.

   The patient will then be remotely asked to reproduce the DIBH maneuver with the tolerance window to which they have been assigned and be treated in DIBH. Number of beam holds, treatment interruptions and total treatment time from first beam-on time to the last beam-off time will be recorded by the therapists. Beacon position during DIBH will be monitored by the therapist to assure that the patient maintains the DIBH position throughout the treatment delivery. If the Calypso beacon signal indicates that the tumor has moved outside of the tolerance window, the radiation beam will be automatically held by the system and resumed when the target is within range.

9.2 For patients undergoing standard fractionated RT the following procedures will be performed:

1. Standard setup procedures based on external tattoos will be performed.

2. The Calypso antenna will be deployed and positioned over the patient's chest. Tracking of the Calypso transponder signal will commence.

   Optional: In patients where the Calypso antenna external markers detected by an in-house infrared tracking system can be arranged in such a way that both signals can be obtained

simultaneously (depending on body habitus), a free-breathing trace of the Calypso transponders over 2 minutes in combination with the external marker signal will be obtained . These will be used for future analysis and building of an external/internal respiration model.

3. For patients who have been selected to use the digital goggles, the DIBH maneuver will be performed with visual biofeedback at least once a week and at least one fraction will be done without visual feedback .During treatment the radiation therapist will coach the patient on how to hold their breath during the treatment. On treatment days with visual feedback, the patient will be able to view and control his/her breathing through biofeedback using goggles (Myvu Personal Media Viewer, Myvu Corporation) or an iPhone that displays the Calypso trace. The couch position will be adjusted by the therapists in the treatment room to accurately set up the patient for treatment in DIBH based on the Calypso signal. The Calypso trace will be set to zero based on the DIBH level.

4. The patient will resume regular breathing and the therapists will leave the room.

5. The patient will be remotely asked to repeat the DIBH maneuver and a set of orthogonal kV images will be obtained. These will be used to verify that no beacon has migrated from its initial position.

7. Once a week, the patient will be remotely asked to repeat the DIBH maneuver and a CBCT will be obtained over several breathholds (exact number depending on the patient's ability to hold their breath) of 15 seconds each using partial arcs and the assigned breath hold tolerance window. No more than 8 weekly imaging sessions with CBCT will be done for protocol purposes.

8. The CBCT images will be evaluated and the patient will be repositioned for a soft tissue match as needed. The soft tissue match will then be evaluated and approved by the treating physician. The isocenter coordinates in Calypso will be changed based on the patient's repositioning shift dictated by the CBCT soft tissue match.

   The patient will then be remotely asked to reproduce the DIBH maneuver with a tolerance window to which they have been assigned and be treated in DIBH Number of beam holds, treatment interruptions and total treatment time from first beam-on time to the last beam-off time will be recorded by the therapists. Beacon position during DIBH will be monitored by the therapist to assure that the patient maintains the DIBH position throughout the treatment delivery. If the Calypso beacon signal indicates that the tumor has moved outside of the tolerance window, the radiation beam will be automatically held by the system and resumed when the target is within range. For treatments between CBCT sessions, the patient will be set up according to steps 1-4, kV images will be acquired (Step 5) to verify beacon stability and the day's treatment with breath-hold will proceed without further imaging.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Physician evaluation of patient setup accuracy will be performed using all available images and adjustments will be made as per standard practice. In addition, the Calypso signal will be used to verify and monitor the patient's DIBH maneuver. Should the transponder signal indicate that the target has moved outside of the preset tolerance, radiation treatment delivery will be held until the patient's breathhold has returned to the desired target range or until the patient's setup has been corrected.

Patients will return for follow up at 3, 6, 9 and 12 months(+/- 4 weeks) following completion of radiation therapy. Data from any clinical followups between 12 and 24 months following completion of radiation therapy(+/- 4 weeks) will be collected retrospectively through a retrospective research protocol. The following assessments will be performed at these visits: history and physical exam, diagnostic CT chest, and toxicity assessment. The history and physical exam may be completed in the medical oncology clinics for patients who experience progression of disease. In this case, the toxicity assessment will be completed over the phone with the treating radiation oncologist.

	Pre-treatment	Simulation	Radiation Treatment (SBRT)	Radiation Treatment (standard fractionation)	Follow-up 3, 6, 9 and 12 months
History & physical	x				x
Pregnancy test (if applicable)	x				
Evaluation for DIBH fitness	x				
Beacon implantation	x				
CT scan for navigation	x				
Free-breathing scan		x			
4DCT		x			
DIBH CT		x			
Set-up			x	x	
Calypso signal recording			x	x	
RT with DIBH with or without visual feedback			x	x	
Daily Orthogonal KV images				x	
Weekly CBCT (up to 8)				x	

Daily CBCT (up to 2 CBCTs per fraction for protocol purposes)			**x**		
Diagnostic CT chest	x				x
Toxicity assessment			Weekly during treatment	Weekly during treatment	x

11.0 TOXICITIES/SIDE EFFECTS

Patients will be monitored for study-related toxicities according to CTCAE v4.0. Only side effects that are possibly, probably or definitely related to the protocol therapy and grades 2-5 will be documented. This includes the following toxicities:

1. Potential side effects related to anesthesia:
    a. Hypotension
    b. Arrhythmia
    c. Respiratory failure
2. Potential side effects related to flexible bronchoscopy:
    a. Sore throat
    b. Post-extubation bronchospasm
    c. Throat or chest tightness
3. Potential side effects related to the implantation and/or the fiducial markers:
    a. Bronchopleural fistula
    b. Lung or airway damage
    c. **Bleeding**
    d. Fever
    e. Hemoptysis
    f. Respiratory infection / pneumonia
    g. Lung Infection
    h. Pneumothorax
    i. Cough
    j. Dyspnea
    k. Fiducial embolization
    l. Migration of fiducial markers
4. Potential side effects related to radiation therapy:
    a. Fatigue
    b. Cough

c. Dyspnea
d. Pneumonitis
e. Dysphagia
f. Esophagitis
g. Nausea
h. Vomiting
i. Diarrhea
j. Anorexia
k. Dehydration
l. Radiation dermatitis
m. Respiratory infection / pneumonia

Abnormal laboratory values, regardless of grade, will not be reported. Toxicities of treatments that are not associated with the protocol therapy (i.e. chemotherapy-related side effects) will not be graded nor attributed.

Only toxicities communicated directly to, and reviewed by, the treating physician or study PI, and deemed possibly, probably or definitely related to the protocol treatment will be documented.

A clinical study summary can be found at: http://oncology.varian.com/calypsolungstudy

DEFINITIONS

1. Definition of an Adverse Event (AE)
    a. An Adverse Event is defined by the GCP (Guide to Good Clinical Practice) as any undesirable experience occurring to a subject during a clinical trial, whether or not it is considered related to the investigational product(s).

2. Definition of a Serious Adverse Event (SAE)

    a. A Serious Adverse Event is an adverse experience that:

        i. is fatal or life-threatening

        ii. is disabling

        iii. results in hospitalization or prolongation of hospitalization

        iv. results in a congenital anomaly or occurrence of malignancy

    b. Any neurologic and musculoskeletal toxicity that is grade 3 or higher will be considered a serious adverse event.

c. Only serious adverse events that are at least possibly related to the investigational product will be reported as the radiation therapy is considered standard of care.

3. Definition of an Unexpected Adverse Event

a. An Unexpected AE is an experience not previously reported (in nature, severity, or incidence) in the current Investigator's Brochure or general investigational plan.

Evaluation of SAE:

Review of the patient record including the treatment dosimetry will be undertaken by the principal investigator. The principal investigator may decide to continue the protocol without modification, discontinue the study altogether, or to modify the protocol prior to enrolling more patients pending the results of the review. However, if the SAE meets the criteria for the stopping rule, as defined in Section 14.0, the trial will be stopped.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Primary objectives:

- To evaluate the feasibility of Calypso transponders as an internal tumor surrogate to guide DIBH radiation treatments in real time.

- Feasibility is defined as completion of all treatments using the DIBH treatment plan and Calypso transponders. Patients who cannot have their transponders placed accurately bronchoscopically or for whom Calypso-guided DIBH will not be possible will be considered a failure. Patients who are removed from the protocol as a result of being unable to perform the breath hold for 3 consecutive treatment days at any point in the treatment course for reasons that are not related to the Calypso transponders, Calypso detection or complications of using the Calypso implantation or system (e.g. disease progression, severe side effects from treatment, e.g. esophagitis, infections, failure to thrive, generalized weakness, low blood counts etc.), will be replaced by new evaluable patients. Those patients will be treated with the free-breathing backup radiation treatment plan. The reason for the patient's inability to hold their breath will be recorded.

Secondary objectives:

- To compare the reproducibility with visual versus without visual biofeedback.
- To assess differences in the ability of maintaining the DIBH maneuver within the fate with and without visual biofeedback
- To measure the residual intrafraction tumor motion and associated improvement in normal tissue dosimetry during DIBH based on the Calypso lung transponder signal as a surrogate

  - To measure the increase in dose escalation and the potential for decreasing margins made possible by Calypso-guided DIBH
- To determine the minimum clinically feasible gate margin for radiation
- To assess tumor shrinkage, beacon position and centroid changes in conventionally fractionated patients
- To assess intra- and inter-fraction variation in lung volume preservation of multiple DIBH maneauvers

Reproducibility of using internal tumor surrogates (Calypso beacons) during repeated deep inspiration breath hold maneuvers with and without visual biofeedback will be evaluated by posthoc analysis of the Calypso signal traces. The ability to maintain the breathhold to within the tolerance level to which they have been assigned will be assessed. Number of beam holds and treatment interruptions will be recorded as an objective measure of the patient's ability to maintain their breathhold. Whether or not visual biofeedback will aid in the ability to hold their breath reliably and within the target region will be assessed using the number of treatment interruptions. We will also assess differences in duty cycle and number of DIBH attempts with and without visual biofeedback. Differences in the ability of maintaining the DIBH maneuver within the gate with and without visual biofeedback will be measured as duty cycle, a quantifiable measure of how long it takes to deliver a radiation treatment. It is related to how well patients can hold their breath and the tumor in the target position. Each patient will have the goggles 50% of the treatments and without goggles the other 50% of the time. Wilcoxon rank sum tests will be done to compare the duty cycle.

The residual intrafraction motion and drift during DIBH will be determined based on the Calpyso signal traces which may provide critical insight into the ability to immobilize the tumor by DIBH. Beacon position stability will be determined on acquired cone-beam CTs by measuring the distance of the beacons to the center of the gross target volume {GTV) as well as the distance of the beacons to each other. Improvement of normal tissue dosimetry based on Calypso-guided DIBH will be determined from the treatment plans developed on the free-breathing and DIBH simulation CT scans. Specific dosimetric parameters will include the chest wall V30, total lung V20, mean lung dose, lung toxicity model metrics (Lyman model NTCP and parallel model fraction damaged (fdam)), mean and maximum esophageal dose, and maximum spinal cord dose.

To determine the minimum clinically feasible gate margins we will decrease the gate in a step-wise progression as far as a minimum of 2 mm. The gate will be reduced from +/- 5mm by 1mm for every 5 patients treated. Halving of the duty cycle will be considered the minimum gate that is clinically feasible. Once the minimum gate is determined, the remaining patients will be treated at +1mm from this value.

In the additional 10 conventionally fractionated patients, tumor shrinkage will be summarized as relative shrinkage in a percentage. Beacon position and centroid are 3D coordinates that will be determined as a distance from a landmark such as a bone or the carina.

Lung volume preservation will be assessed on wide field of view cone-beam CTs and compared intra- and interfraction within each patient to check for reproducibility or variability of lung volumes across multiple DIBH maneuvers.

13.0 CRITERIA FOR REMOVAL FROM STUDY

1. Found to be ineligible for the protocol as described in the section on Criteria for Patient/Subject Eligibility
2. Patient and/or guardian requests to withdraw from study for any reason
3. Referring physician requests to withdraw from study for any reason, including believing that it would be in the patient's best interest
4. Refusal of patient to continue treatment and/or observations
5. Loss to follow-up
6. Patient death
7. Calypso beacon migration of >5cm from original implantation position may be taken off study if the Calypso signal can no longer be detected
8. Patient unable to adequately perform the breath hold for 3 consecutive treatment days

Acquired data from patients who would be removed from the protocol after a portion of the treatment has been completed can be used for analysis.

14.0 BIOSTATISTICS

The primary objective of this nonrandomized study is to test the feasibility of anchored Calypso transponders to guide and monitor DIBH radiation treatments. Feasibility is defined as patients being able to successfully complete the course of treatment. Patients who cannot have their transponders placed accurately bronchoscopically and for whom Calypso-guided DIBH will not be possible as a consequence of that will be considered a failure. Patients who are removed from the protocol as a result of being unable to perform the breath hold for 3 consecutive treatment days at any point in the treatment course for reasons that are not related to the Calypso transponders, Calypso detection or complications of using the Calypso implantation or system (e.g. disease progression, severe side effects from treatment, e.g. esophagitis, infections, failure to thrive, generalized weakness, low blood counts etc.), will be replaced by new evaluable patients. The patients who are removed will be treated with the free-breathing backup radiation treatment plan. The reason for the patient's inability to hold their breath will be recorded.

For this objective the first and second set of 25 evaluable patients will be stratified and analyzed separately. Some details are provided below.
We will enroll 30 patients upfront and we expect that at least 25 evaluable (DIBH training can be done and Calypso beacons can be implanted without migrating > 5cm) patients can be used in

assessing the feasibility rate. To establish the decision rule we will compute the sample feasibility rate (i.e., the number of patients who could be successfully treated divided by the total number of evaluable patients, which we expect to range from 25 to 30) and form an 80% 2-sided Clopper-Pearson exact confidence interval. If the lower bound of this exact confidence interval is greater than 66% then we will declare this procedure feasible. Namely, we will test the hypotheses Ho: 9<=0.66 vs. H1: 9>0.66 at alpha=0.05, where 9 denotes the feasibility rate. The test statistic will be the lower bound of the 90% 2-sided Clopper-Pearson exact confidence interval for binomial trials. Equivalently, this test statistic can be written as Beta(0.05, X, N+1-X), i.e., the 5th-percentile of the beta distribution with two parameters X and N+1-X, where X and N denote the number of successes and the total sample size (expected to be from 25 to 30), respectively. When the sample size is as small as 25, the power of rejecting the null hypothesis is 61%, 84% and 97% when the true feasibility rate is 0.80, 0.85 and 0.90, respectively. When the sample size is as large as 30, such power becomes 61%, 85% and 97%. Since we expect the feasibility rate to be around 0.85, the sample size is sufficiently large. We expect to finish the recruitment in 4 years.

For protective purposes we will implement a stopping rule to prevent excessive rate of pneumothorax or hospitalization (related to the proposed procedure). If 6 or more events (i.e., procedure-related pneumothorax or hospitalization) among the first 30 patients, or 11 or more events among the total 55 patients we plan to enroll are observed, we will halt the trial to thoroughly investigate such events. This sequential stopping rule has the following probability of halting the trial:

True event probability	0.05	0.08	0.10	0.15	0.20	0.25	0.30
Probability of halting the trial	0.003	0.030	0.081	0.342	0.679	0.900	0.978

In addition, a second stopping rule will be implemented if a maximum of two device migrates to a critical organ, such as the heart or brain, or if one device-related death is observed.

For the 1st secondary objective, we will compare the visual vs no visual biofeedback treatments (for patients who agree to use the digital goggles) by the number of treatment interruptions. We expect that there will be fewer treatment interruptions when using biofeedback. To this end Wilcoxon signed-rank tests will be conducted based on the patients who can successfully be treated.

For the 2nd secondary objective, we will assess differences in the ability of maintaining the DIBH maneuver within the fate with and without visual biofeedback. Such differences will be measured as duty cycle, and will be compared using Wilcoxon signed-rank tests based on the patients who can successfully be treated.

For the 3rd secondary objective, the residual intrafraction tumor motion (surrogated by Calypso) will be measured in all 3 dimensions and the euclidean distance will be calculated, which will then be correlated with the normal tissue dosimetry (see end of Section 12.0). Patients will receive multiple fractions and thus multiple measurements of such distance will be obtained from the same patients.

These repeated measures will be averaged for each patient and the correlation will be examined by simple linear regression. If such continuous data are skewed, we may either use an appropriate monotone transformation, or examine the nonparametric correlation coefficient (such as Spearman rank correlation coefficient) between the tumor motion and the normal tissue dosimetry instead.

For the 4th secondary objective, the potential increase in dose escalation and decrease in margins made possible by Calypso- guided DIBH, as contrasted to those obtained from the 40 CT scan, will be formulated as pair data from each patient and tested by using Wilcoxon signed-rank tests. Dosimetric parameters listed at the end of Section 12.0 will be used again for such analysis.

The 5th secondary objective does not require statistical analysis. See Section 12.0 for details.

For the 6th secondary objective, tumor shrinkage, beacon position and centroid changes in conventionally fractionated patients (totally 10), all measured as continuous variables, will be summarized descriptively.

For the 7th secondary objective, intra- and inter-fraction variation in lung volume preservation of multiple DIBH maneauvers will be recorded within each patient and summarized descriptively.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming that the participant is eligible to enroll in the study. Study *staff* are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

No randomization will occur in this study.

16.0 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator (CRC) and/or Clinical Research Associate (CRA) will be assigned to the study. The responsibilities of the CRC or CRA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Regular registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at:

http://mskweb2.mskcc.org/irb/index.htm

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board. During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Risks: There are small risks of side effects related to the implantation of the Calypso transponders into small airways near the tumor or the tumor itself. These risks include but

are not limited to fever, bleeding, airway obstruction, pneumothorax, device embolization, device migration and pneumonia. Radiation exposure due to additional protocol imaging is minimal. Doses required for kV conebeam imaging are on the order of 3-4 cGy per scan; doses for standard radiographic imaging are less than 0.1 cGy /image.

Costs: All of the treatments, studies, and procedures are considered standard of care, including the placement of standard fiducials for radiation therapy. The patient and/or patient's insurance will be responsible for all charges, which are part of the standard of care. No financial reimbursement or other financial incentive will be provided for patients to enroll in this study. The Calypso beacons will be provided by Varian and are research non-billable. The implantation of the beacons will be billable to insurance. Any complications from the Calypso beacon implantation will be managed as per responsible physician and any tests or interventions related to the management of potential complications will be billed to the patient's insurance. Performing the placement of the Calypso beacon transponders in the context of a clinical trial will allow for a more indepth and objective evaluation of the system.

Benefits: There is a potential clinical benefit from this clinical trial in terms of decreased toxicity from radiation treatments and/or achieving a higher total treatment dose due to DIBH. We hope that in the future, knowledge from this trial will help patients that are candidates for the implantation of Calypso transponders as well as patients who are not candidates by improving our understanding of real-time tumor position changes with respiration.

Side effects: Side effects of the study specific to the implantation of the fiducial markers are anesthesia risk, bleeding, infection, pulmonary toxicities, and migration of the fiducial markers.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).
The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office

per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols:
The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.2.1

Not applicable

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent

form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

Appendix 1:
Patient Instructions: Beacon care package- Lung instructions