Pilot Study of a Novel Optical Surface Image Guidance System for Beam-Gated Online Adaptive SBRT Delivery in Mobile Lower Lung and Upper Abdominal Malignancies

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Protocol Revision History

Initial Approval Version	**07/27/2021**
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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

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PROTOCOL SUMMARY

Title:	Pilot Study of a Novel Optical Surface Image Guidance System for Beam-Gated Online Adaptive SBRT Delivery in Mobile Lower Lung and Upper Abdominal Malignancies
Study Description:	Motion during radiation therapy can be categorized as inter-fraction (changes in anatomy that occur between treatment days) and intra-fraction (changes that occur during the "beam on" window of treatment delivery). Inter-fraction motion is managed by adaptive radiotherapy (ART), the process of making changes in the treatment plan while the patient remains on the treatment table. This is now a standard-of-care therapy within our clinic. Intra-fraction motion is managed by gated and non-gated delivery techniques. Varian Medical Systems has integrated the necessary components into a CT-guided radiotherapy device (ETHOS). In the ETHOS, Varian has built a device that integrates on-board cone beam CT imaging capable of delineating target and organ-at-risk positions and a dedicated artificial intelligence-driven treatment planning system for inter-fraction motion management as well as a paired optical surface image guidance system for intra-fraction motion management. Although online ART is a standard-of-care practice in our clinic and has previously been shown to be feasible, use of surface-guidance for intra-fraction gating of abdominal and thoracic SBRT on ETHOS is novel. Therefore, in this study, we propose to evaluate the feasibility and safety of using a novel surface guidance beam-gating system, incorporated with a CBCT-guided adaptive radiotherapy platform, to manage respiratory motion during delivery of CT-guided stereotactic radiotherapy. To best assess the utility of this technology to manage respiratory motion, we will focus on disease sites that are highly affected by respiratory motion: upper abdominal or lower thoracic malignancies.
Objectives:	<u>Primary Objective</u>: To demonstrate that surface guided, breath-hold respiratory gated delivery of CT-guided stereotactic adaptive radiotherapy (CT-STAR) is feasible in the abdomen and lower thorax by confirming that gated treatment can be delivered successfully in more than 75% of scheduled treatment fractions using a novel surface guidance system. <u>Exploratory Objectives</u>: 1. Determine geometric agreement between breath-hold positioning as determined by a novel surface guidance system vs. concomitant breath-hold CBCT image sets.

	2. Evaluate the compatibility of a standard-of-care respiratory gating system and the novel surface-guidance system for concomitant use. 3. Determine the minimum safe planning target volume and planning organ-at-risk volumes to be subsequently utilized with the novel surface guidance system. 4. Determine the local, in-field control rate at three months post-treatment. 5. Determine acute toxicity rates at three months post-treatment. 6. Identify patient and or treatment factors that maximize the potential efficacy of surface guided breath-hold respiratory gating.
Endpoints:	<u>Primary Endpoint</u>: Percentage of scheduled treatment fractions delivered successfully using the surface guidance system. Success will be defined as delivery of a given treatment fraction in one on-table attempt, without requiring use of a secondary (backup) motion management system, or alternative treatment machine. Unsuccessful delivery of a fraction will be defined as multiple attempts for gating without reproducible positioning, breath-hold, and/or surface guidance feedback, such that the fraction is abandoned. <u>Exploratory Endpoints</u>: 1. Geometric agreement between breath-hold positioning as determined by a novel surface guidance system compared with standard of care concomitant breath-hold CBCT image sets, as evaluated by average symmetric surface distance (ASSD), modified Hausdorff distance (MHD), and Dice similarity coefficient measurements. 2. Qualitative evaluation of the compatibility of a standard-of-care respiratory gating system and the novel surface-guidance system for concomitant use. 3. Quantitative and qualitative measurement of minimum planning target volume (PTV) margins and planning organ-at-risk volumes to be subsequently utilized with the novel surface guidance system as determined through measurement evaluations in exploratory endpoint 1. 4. Local, in-field control rate at three months post-treatment will be determined as part of standard-of-care clinical evaluation by the treating physicians, using RECIST criteria. 5. Qualitative description of acute (within 90 days) Grade 3 or higher non-hematologic toxicity events related to radiation therapy at three months post-treatment. 6. Qualitative description of patient and treatment site factors, such as unique patient surface topography or skin tone, that

	might impact surface imaging tracking at the region of interest.
Participant Population	Ten adult patients with upper abdominal or lower thoracic malignancies who will be treated with CT-guided stereotactic radiotherapy with optional online adaptation and surface-guided beam-gating.
Phase:	N/A (device feasibility)
Description of Sites / Facilities Enrolling:	This study will be open at the Siteman Cancer Center at Washington University School of Medicine.
Description of Study Intervention:	The Varian ETHOS is a ring-gantry CT-guided radiotherapy unit. It pairs a linear accelerator within a ring-gantry imaging unit. It has an on-board cone beam CT imaging unit capable of delineating target and organ-at-risk position and a dedicated AI-driven treatment planning system to enable online adaptive radiotherapy. Recently, it has also been paired with an optical surface image guidance system (the Identify OSIG) which relies upon a time-of-flight, ceiling mounted, stereo camera system and a random pattern projector. A random light pattern is projected onto the patient's surface, the reflection of which is captured by the stereoscopic cameras with subsequent calculation of a 3D point cloud based on corresponding points identified across the camera set. A surface region of interest is selected and then monitored for motion or deformation. This has been utilized previously for surface-based radiation delivery, such as for breast cancer, but has not previously been utilized to guided stereotactic body radiotherapy (SBRT) for internal thoracic or abdominal targets as part of the Varian ETHOS treatment platform. In this pilot/Phase I study, the feasibility and safety of using the Identify OSIG system to guide delivery of thoracic and abdominal SBRT will be evaluated. Consenting and eligible patients will be treated using SBRT in five fractions over one to two weeks. For patients undergoing optional plan adaptation, adaptation will be based on daily anatomic changes as per standard of care. For both adaptive and non-adaptive patients, the prescription dose will be determined based on normal tissue constraints and capped at 12 Gy per fraction, as per standard institutional practice.
Study Duration:	12 months (enrollment) + 2 weeks (treatment) + 3 months (follow-up) + 12 months (analysis) = 28 months
Participant Duration:	4 months

1.0 BACKGROUND AND RATIONALE

1.1 SBRT for tumor ablation

Within the realm of radiation therapy, stereotactic body radiotherapy (SBRT) has emerged as a means to focally target and ablate both primary and metastatic cancers [1]. This technique involves delivery of numerous, individually weak radiation beams to converge on a focal target for delivery of a highly precise, conformal, and ablative dose in five or fewer treatment fractions. The dose per fraction is substantially higher than that used in conventionally fractionated radiotherapy, where treatment fields tend to be larger, may overlap with normal tissues, and are treated in small amounts of radiation per day over multiple (usually 5 or more) weeks of therapy. The high dose per day used for SBRT--unthinkable in the prior era—is enabled by progressive advancement in treatment delivery and image-guidance technology that allows safe, accurate, and precise treatment delivery. Compared to conventionally fractionated radiotherapy, SBRT has been shown to improve overall survival outcomes in early stage non-small cell lung cancer[2] and is associated with improved overall survival in upper abdominal cancers like pancreatic cancer [3,4]. Similarly, when compared to standard systemic therapies or conventional care, focal disease ablation with SBRT also improves overall survival in oligometastatic cancers of multiple histologies [5-7].

The efficacy of SBRT in producing durable disease control and survival benefit is predicated on delivery of sufficiently ablative dose. Dose escalation, particularly to dose thresholds achieving a biologically effective dose (BED) of 100Gy or more, has been demonstrated to improve local control and survival outcomes across histologies [8-10]. Delivery of such high dose treatment depends on focal target delineation and rapid radiation dose fall off to avoid excess dose to surrounding normal tissues. Excess dose to adjacent critical structures erodes the therapeutic gain of SBRT over conventional fractionation and can result in high grade toxicity and even mortality risk [11]. Thus, precise SBRT delivery and minimized dose to surrounding organs-at-risk (OARs) is critical. This balance of the therapeutic index is particularly challenging in treatment sites subject to motion, especially when critical structures are proximal to the tumor. Indeeed, in such cases, adequate treatment of the tumor with necessary margins to account for its possible locations in a four-dimensional (4D) space can then compete with the space occupied by adjacent OARs and their similar motion.

1.2 SBRT Considerations for Mobile Tumors

Motion during radiation therapy can be broadly categorized as being inter-fraction or intra-fraction. Inter-fraction motion comprises less-predictable changes in anatomy that occur in between treatment days, such as normal organ motion from peristalsis (e.g., bowel peristalsis) or organ filling (bladder, stomach, rectum), or changes like tumor shrinking response to treatment. Intra-fraction motion refers to the motion occurring during the "beam on" window of treatment delivery. Predictable motion from the respiratory cycle is a dominant contributor to intra-fraction motion during SBRT to thoracic and abdominal

tumor sites and is a common focus of intra-fraction motion management. In order to maximize the therapeutic index for SBRT delivery, one ideally considers and manages both types of motion.

1.3 Inter-fraction Motion Management

Until recently, inter-fraction motion management options to adjust for changes in tumor and organ-at-risk geometry in between treatment days have been limited. This motion is often unpredictable, such as with peristalsis, or difficult to control even with explicit instructions to patients, such as bladder filling. It can also be due to more permanent changes in patient anatomy, like reduction in tumor size during treatment or patient weight loss. Management of such semi-permanent inter-fraction changes has relied inconsistently on o*ffline* adaptation, or changes made to the radiation treatment plan in the hours between deliveries, while the patient is *off* of the treatment table. Offline ART is most commonly utilized in head and neck cancer radiotherapy for tumor response and patient weight loss [12]. In contrast, a plan library approach attempts to address more dynamic (but still predictable) motion like organ filling. It involves creation of several plan choices for a single patient, so that depending on the "anatomy of the day", the best-matching plan is crudely selected for delivery. This is best described in pelvic radiotherapy to mitigate the impact of bladder filling changes on target coverage and OAR sparing [13,14]. However, neither offline nor plan library adaptive approaches permit flexible real-time adjustment of treatment plans and neither accounts for unpredictable motions, like peristalsis.

Online ART is well-suited to account for both unpredictable and predictable types of inter-fraction motion. Online ART defined as the process of making daily changes in the radiation therapy treatment plan in response to observed changes in daily anatomy, while the patient remains on the treatment table. Our institution was the first in the world to clinically implement this technique for SBRT in 2014, using advanced image-guidance with magnetic resonance imaging [15,16]. In the setting of SBRT, this allows the treating physician to account for and respond to inter-fraction organ motion and tumor changes to maximize tumor dose while minimizing dose to normal tissue. This improves the precision and accuracy of SBRT delivery and widens the therapeutic index. Specifically, our institution and others have shown improvement in the dosimetric therapeutic index of SBRT using online ART for upper abdominal [16], thoracic [17], and pelvic disease sites [18]. This has translated into prospectively and retrospectively validated reduction in treatment-related toxicities and is associated with improvement in local control and survival outcomes [4,18,19].

Efficient delivery of online ART requires three key components: 1. on-table imaging sufficient to delineate the target and organs-at-risk, 2. a dedicated treatment planning system (TPS) for rapid on-table treatment plan generation and comparison, and 3. real-time quality assurance of adaptive plans prior to treatment delivery [20]. While online ART can be achieved by existing integrated magnetic-resonance image-guided systems [21] as well as patched-together systems using CT-on-rails and rapid plan exportation outside of a dedicated TPS, these components have now also been successfully integrated into a CT-guided radiotherapy device (ETHOS, Varian Medical Systems, Palo Alto, CA) on a widely

available commercial platform. This CT-guided device received CE MARK and FDA clearance in late 2019 and early 2020 respectively, and has been clinically implemented both at our institution and in Europe. Improved access to the online adaptive planning techniques through this high-through-put, integrated, and commercially available CT-guided radiotherapy system is likely to further advance the use of online ART for inter-fraction motion management in the global clinic.

1.4 Intra-fraction Motion Management

Unlike inter-fraction motion, which can be addressed at a single daily pre-treatment time point using online ART, intra-fraction motion management requires continual management of motion actively occurring throughout the beam-on time of daily treatments. The dominant contributor to intra-fraction motion in affected sites like the thorax and abdomen is the predictable motion of the respiratory cycle [22].

1.4.1 Non-gated delivery techniques

In some mobile sites, where respiratory motion amplitude is smaller and occurs away from organs-at-risk, the full positional range of the tumor (the "internal target volume", or ITV) can be determined using 4-dimensional CT planning images. In this common approach for upper and middle lung lesions, 4DCT at time of simulation simultaneously acquires spatial and temporal information on mobility and shape of a tumor. From this, reconstructed imaging data can be binned according to respiratory phase and used to generate the ITV according to imaging reconstructions like the maximum intensity projection (MIP) or average intensity projection (AIP), with further editing to ensure the tumor is fully encompassed by the ITV in all phases of breathing [23,24]. Physical interventions like use of abdominal compression plates can be complementarily used to limit ITV size by limiting the amplitude of respiratory excursion and have been shown to reduce motion in the SI plane by up to 50% [25]. Nevertheless, in such sites, one still accepts that the ITV motion envelope expands the ablation target into low-risk normal tissues, like normal surrounding lung parenchyma, in order to capture the full extent of tumor location during delivery.

1.4.2 Gated Delivery Techniques

In sites where respiratory motion amplitude is larger, such as in the lower lobes of the lung or the upper abdomen, gated treatment delivery may be utilized instead in order to avoid excessive intentional treatment of normal tissues. Respiratory beam-gating comprises turning the treatment beam on and off as the tumor moves in and out of the radiation beam path with respiration during treatment delivery. This may be phase (e.g. end-exhale breath-hold) or amplitude based or be triggered based on implanted internal fiducial marker tracking. In lung patients, the typical threshold to trigger gated delivery as opposed to using an ITV approach is a measured tumor respiratory motion amplitude of >1cm despite adequate abdominal compression at the time of simulation image acquisition (PACIFIC-4 protocol) TG 101. In the

abdomen, where surrounding tissues are at higher injury risk, e.g., the duodenum relative to the pancreas [26], and/or the 4D motion envelope of a tumor may have ill-defined margins, gated delivery of SBRT is a common approach [27-29].

Gated delivery of SBRT requires real-time monitoring of respiratory motion, most often using surrogates for the tumor motion. This can be accomplished using several technologies. One standard technique is real-time position management (RPM), with an infrared camera system mounted in the treatment room that monitors the movement of a reflective surrogate external marker block placed on the patient's abdomen or chest [30]. A respiratory trace is generated based off of tracked surrogate motion and the beam can be gated on and off at desired phases or amplitude ranges of the respiratory cycle. However, use of a single external marker box alone to capture motion in a single plane may not robustly account for respiratory motion of an internal target and can result in errors in target localization of ~5mm in the SI plane[31]. RPM can be used in combination with periodic triggered intra-fraction imaging visualization of the tumor or internally placed fiducial markers to verify consistent correlation between the tumor and surrogate motion and improve accuracy, although an additional 2-3mm of uncertainty may remain [31,32]. While more robust, fiducial placement and monitoring or even fiducial tracking-based deliveries are expensive, require an invasive procedure for fiducial implantation, lead to delays in initiation of treatment for marker placement and settling before simulation [28], and expose the patient to protracted treatment times [33] as well as additional imaging dose during delivery [34].

An alternative and emerging technique is the use of optical surface image monitoring for continuous, non-invasive, and non-radiographic patient localization and respiratory tracking for SBRT. Surface guided radiotherapy can enable both breath-hold and amplitude phase-based gating, using a combination of light projectors to project a pattern of light onto the patient's surface and 2-3 optical cameras to generate and then track the motion of a 3-dimensional map of patient topography. Compared with techniques like RPM, monitoring of multiple surface points instead of a single surrogate marker improves accuracy of motion monitoring [35]. Surface guidance motion monitoring has been shown to be accurate to 1mm motion/1degree of rotation in the delivery of intracranial stereotactic radiosurgery [36]. It is also used to enable deep inspiratory breath hold (DIBH) gating in focal radiotherapy treatments like accelerate partial breast radiotherapy (APBI) to within 2mm of setup accuracy [37]. Recently, it has been implemented for monitoring of internal target motion for lung and upper abdomen SBRT, and shown to accurately reflect internal anatomic shifts of 2mm or more compared to repeat cone beam CT alignment [25 38].

1.5 Varian ETHOS system

Ideally, to maximize the therapeutic index of SBRT, both inter- and intra-fraction motion management strategies would be combined within a single treatment platform. This combination is now possible using a novel CT-guided radiotherapy device. Varian Medical

Systems (Palo Alto, CA) has produced a unique ring-gantry CT-guided radiotherapy unit, pairing a linear accelerator within a ring-gantry imaging unit. In addition to housing an on-board cone beam CT (CBCT) imaging unit capable of delineating target and OAR positions [39] and dedicated artificial-intelligence (AI)-driven TPS to enable online adaptive radiotherapy, this system also has a paired optical surface image guidance system for intra-fraction motion management. Our institution is among the first in the world to use this device for standard of care patient treatment, having completed commissioning and testing of treatment planning software, dose delivery, and imaging technology. Its online adaptive radiotherapy capabilities (for inter-fraction motion management) have already been established in non-mobile sites. Similarly, the paired Identify OSIG system has been evaluated for conventionally fractionated radiotherapy treatment. However, the OSIG system has yet to be prospectively evaluated for beam-gating specifically during SBRT.

1.6 Identify Surface Guidance system

The Identify system relies upon a time-of-flight, ceiling mounted, stereo camera system and a random pattern projector. A random light pattern is projected onto the patient's surface (e.g., abdominal or thoracic wall), the reflection of which is then captured by the stereoscopic cameras with subsequent calculation of a 3D point cloud based on corresponding points identified across the camera set. A surface region of interest (ROI) is selected and then monitored for motion or deformation. Motion of the respiratory cycle can be tracked in this manner and used to derive a phase-based respiratory trace for on-off gating of the radiation beam at particular respiratory phases, such as DIBH and end-exhale.

A recorded surface can be calculated at time of patient planning simulation and used for initial patient alignment on days of treatment, with subsequent updating of both the reference surface and patient alignment based on the initial daily setup verification CBCT acquired in room. This new daily surface ROI can then be monitored for intra-fraction respiratory motion management through beam-gating, with SGRT software calculation of differences in the patients' actual surface vs. the daily reference surface. The respiratory trace is utilized by the treatment team to gate the beam on and off, with available use of visual feedback of the respiratory trace to the patient (through an institutional in-room display monitor or patient goggles) for respiratory coaching. The patient can then be treated in a series of end-exhale or DIBH breath-holds, with optional CBCT verification of patient position at pre-set intervals during treatment.

1.7 Study Rationale

In light of this new motion management technology, we propose to evaluate the feasibility and safety of using a novel surface guidance beam-gating system, incorporated with a CBCT-guided adaptive radiotherapy platform, to manage respiratory motion during delivery of CT-guided stereotactic radiotherapy. To best assess the utility of this technology to manage respiratory motion, we will focus on disease sites that are highly affected by respiratory motion. Specifically, we will enroll patients with upper abdominal or lower thoracic malignancies to receive CT- guided stereotactic radiotherapy with optional online adaptation and surface-guided beam-gating. Patients will be treated in five

fractions over one to two weeks. For patients undergoing optional plan adaptation, adaptation will be based on daily anatomic changes as per our clinical standard of care. For both adaptive and non-adaptive patients, the prescription dose will be determined based on normal tissue constraints, and capped at 12 Gy per fraction. By adhering to standard institutional normal tissue constraints and gating window parameters, expected toxicity will be within the current standard of care. Feasibility of using the Identify optical surface guidance system to gate stereotactic treatment of the upper abdomen and lower thorax has never previously been reported and will be the primary goal of the present study.

2.0 OBJECTIVES

2.1 Primary Objective

Demonstrate that surface guided, breath-hold respiratory gated delivery of CT-guided stereotactic adaptive radiotherapy (CT-STAR) is feasible in the abdomen and lower thorax by confirming that gated treatment can be delivered successfully in more than 75% of scheduled treatment fractions using a novel surface guidance system. Success will be defined as delivery of a given treatment fraction in one on-table attempt, without requiring use of a secondary (backup) motion management system, or alternative treatment machine. Unsuccessful delivery of a fraction will be defined as multiple attempts for gating without reproducible positioning, breath-hold, and/or surface guidance feedback, such that the fraction is abandoned.

2.2 Exploratory Objectives

1. Determine geometric agreement between breath-hold positioning as determined by a novel surface guidance system vs. concomitant breath-hold CBCT image sets.
2. Evaluate the compatibility of a standard-of-care respiratory gating system and the novel surface-guidance system for concomitant use.
3. Determine the minimum safe planning target volume and planning organ-at-risk volumes to be subsequently utilized with the novel surface guidance system.
4. Determine the local, in-field control rate at three months post-treatment.
5. Determine acute toxicity rates at three months post-treatment.
6. Identify patient and or treatment factors that maximize the potential efficacy of surface guided breath-hold respiratory gating, such as differences in surface topography and skin tone.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Primary or metastatic disease of the abdomen or lower thorax, with biopsy-proven or radiographically diagnosed disease histology of solid tumor categorization, with the exception of small cell cancers.

2. Must be medically fit for SBRT as determined by the treating physician, with at least one disease site to be deemed suitable for treatment with CT-guided stereotactic radiation to the abdomen or thorax as per radiation oncologist evaluation.

3. At least 18 years of age.

4. Karnofsky performance status > 60 (see Appendix A)

5. Capable of single deep inspiratory breath-hold or end-exhale breath-hold of at least 17 seconds in duration and of repeated end-exhale or deep inspiratory breath-hold of at least 10 seconds in duration upon verbal instruction.

6. Must have completed any systemic therapy at least one week prior to planned start of SBRT (two weeks preferred), and must have no plans to initiate systemic therapy for at least one week following end of SBRT (two weeks preferred).

7. Able to understand and willing to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. Past history of radiotherapy within the projected treatment field of any of the disease sites to be treated by CT-guided SBRT.

2. Currently receiving any investigational agents.

3. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

4. Pregnant and/or breastfeeding. Patient must have a negative pregnancy test within 14 days of study entry.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center OnCore database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

5.0 TREATMENT PLAN AND DELIVERY

5.1 Radiation Therapy Guidelines

5.1.1 Dose, Fractionation

Radiotherapy will consist of stereotactic body therapy, to be given over five fractions, delivered once daily or once every other day for a period of one to two weeks, for a total of five treatments. Of note, safety of treatment well be kept within established guidelines based on standard institutional constraints applied to normal

tissues. Patients will be planned for a minimum dose of 35 Gy in five fractions to the PTV, with optional dose adaptation based on safety constraints that are already approved of, up to a maximum allowed total dose of 60 Gy in five fractions to the PTV. The maximum allowable prescription dose to the PTV on any day with adaptive planning will be constrained to 12 Gy, subject to coverage goals below.

5.1.2 Simulation Procedures/Patient Positioning

All patients will undergo both CT and CBCT simulation in positioning appropriate for the specific treatment site. When medically feasible and applicable, patients will be simulated with IV and small bowel contrast (for non-thorax cases).

5.1.3 Clinical Target Volume (CTV) and Planning Target Volume (PTV) Definitions

The treatment target will be defined based on the gross tumor volume (GTV) only. No CTV expansion will be utilized, as per standard-of-care procedures in the setting of SBRT. Additionally, no ITV expansion will be utilized, as gated delivery is planned. The PTV will be generated at the discretion of the treating physician but should range between 3 mm and 7 mm.

5.1.4 Initial Treatment Planning

All patients will be initially planned to at least 35 Gy in 5 fractions, subject to hard constraints based on the treatment site. Dose volume histogram (DVH) information for the target volumes and surrounding critical structures is mandatory. This is to assist in interpreting outcome, including morbidity. Coverage goal will be for 95% of the volume to be covered by 95% of the dose, although in situations where a critical structure is violated, reduction of dose will be allowed in areas of overlap.

5.1.5 SBRT Dose Constraints

Standard institutional 5-fraction organ-at-risk dose constraints will be used, at the discretion of the treating physician, and in concordance with the treated (abdomen vs. thorax) site. For those patients undergoing optional plan adaptation, on treatment days where all constraints are met, the prescription dose for that day's treatment may be escalated up to a maximum dose of 12 Gy, if all constraints are met. Adaptive plans will be evaluated under the assumption that the delivered adaptive plan would meet all hard constraints for 5 fractions with stable anatomy. For example, on a given day, the maximum cord dose (to 0.5cc) will be 5 Gy (extrapolate to maximum dose 25 Gy over 5 fractions).

5.1.6 Adaptive Treatment Planning

When patients present for their first SBRT treatment session, patients planned for optional adaptation will be evaluated by the treating physician to determine if

adaptive planning is indicated. Treatment plan re-optimization will be performed for dose adaptation if it is determined that the patient's anatomy allows for dose adaptation with acceptable sparing of normal structures (i.e., not violating the predetermined hard constraints based on safety constraints that are already approved of for routine, clinical use). Dose adaptation can also be done in cases where on the volumetric imaging attained, there is noted to be violation of previously met hard constraints. If there are no violations of any hard constraint, the maximum dose delivered will be capped at 12 Gy per treatment fraction.

5.1.7 Quality Assurance of Adaptive Plans

Patient specific QA will be performed at each fraction prior to delivery of the adaptive treatment plan for any patients undergoing optional dose adaptation. Given that dose measurements will not be possible with the patient on the table, this will be achieved by performing an independent secondary QA check using Mobius. The independent QA will be compared to the dose distribution exported from the ETHOS system, looking at dose volume histograms and 3D gamma analysis of all voxels within the patient. After completion of the automated checks, a final review by physics will be required prior to proceeding to treatment delivery.

5.1.8 Surface-Guided Gated Delivery

At time of CT and CBCT simulation, a baseline reference surface region of interest will be determined. The region of interest (ROI) will be selected on an individual basis for the most sensitivity to detect respiratory motion. At time of first treatment, the patient will be set up to marks and the reference surface. Breath-hold CBCT daily alignment image will be acquired and a new reference surface ROI will be established based on the daily anatomy. The reference surface will be monitored using the Identify system and a respiratory trace will be generated and displayed to the treatment team for breath-hold respiratory gating of treatment delivery. A visual feedback system will be displayed to the patient to aid in respiratory coaching for breath-hold. After treatment alignment and optional adaptation, a repeat breath-hold CBCT will be obtained to evaluate for any patient motion. Shifts can be applied as needed prior to initiation of delivery. CBCT can be repeated in the breath-hold position at set time points, e.g., after each arc in VMAT plans, and at the end of treatment delivery. A recommended maximum of 10 images will be taken per fraction. This will be used for intrafraction patient monitoring as well as subsequent evaluation of concordance between geometric patient position as identified by the Identify system vs. CBCT.

5.2 Evaluability Guidelines

All patients who receive any radiation therapy are evaluable for the primary objective (feasibility of delivering CT-guided SBRT with surface-guidance for gated delivery).

Patients who receive at least one fraction of radiation therapy are evaluable for the

exploratory objectives relating to tumor response/control rate and toxicity.

Success will be defined as delivery of a given treatment fraction in one on-table attempt, without requiring use of a secondary (backup) motion management system, or alternative treatment machine. Unsuccessful delivery of a fraction will be defined as multiple attempts for gating without reproducible positioning, breath-hold, and/or surface guidance feedback, such that the fraction is abandoned.

Should respiratory gating using the Identify optical surface guidance system not be feasible for any given fraction or patient, the treatment fraction will be delivered using an alternative, backup motion management device and/or an alternative linear accelerator as per standard-of-care therapy.

5.3 General Concomitant Medication and Supportive Care Guidelines

Patients are not permitted to receive systemic therapy beginning one week prior to start of SBRT and continuing through SBRT and one week post-completion of SBRT. (It is preferred that patients do not receive systemic therapy within 2 weeks of starting and ending SBRT, but that is left to the discretion of the treating physician.)

5.4 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative pregnancy test within 14 days prior to the start of SBRT.

If a patient is suspected to be pregnant, SBRT should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy, the investigator must be notified in order to facilitate outcome follow-up.

5.5 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue for up to 5 fractions (5 days of SBRT) or until one of the following criteria applies:

- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or

permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

5.6 Duration of Follow-up

Patients will be followed for 3 months following the completion of SBRT or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Follow-up will consist of routine volumetric imaging at 3 months post-completion of SBRT to evaluate treatment response, and evaluation of toxicity 3 months post-completion of SBRT. Any additional follow-up and imaging will be obtained off-study as per routine clinical policies of the treating physician.

5.7 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 3 consecutive scheduled visits and is unable to be contacted by the study team.

The following actions must be taken if the participant fails to return to clinic for a required study visit:
- The study team will attempt to contact the participant and reschedule the missed visit within three weeks of the missed encounter and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as

outlined below. Please refer to Appendix B for definitions and Appendix C for a grid of reporting timelines.

Adverse events will be tracked from start of treatment through 3 months following the last day of SBRT. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF
- Grade 1 adverse events

Refer to the data submission schedule in Section 8 for instructions on the collection of AEs in the EDC.

Reporting requirements for the Washington University study team may be found in Section 6.1.

6.1 WU PI Reporting Requirements

6.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

6.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

6.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 6.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

7.0 STUDY CALENDAR

	Screening	D1	D2	D3	D4	D5	3 mos post-SBRT[4]
Informed consent	X						
Medical history	X						
Volumetric imaging[1]	X						X
CBC	X						
CMP	X						
Pregnancy test[2]	X						
Adaptive SBRT[3]		X	X	X	X	X	
Adverse events assessment[5]		X	X	X	X	X	X
Treatment summary form[6]						X	

1. CT, MRI, or PET are acceptable as per routine clinical evaluation at the discretion of the treating physician
2. Women of childbearing potential only
3. Adaptation of daily SBRT plans is optional
4. Window is 2-4 months post-completion of SBRT
5. Assessment during treatment will be through standard care and standard, weekly on-treatment visits
6. To be completed by the clinical research coordinator

8.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Medical History Form	Prior to starting treatment
Toxicity Form	Continuous
Treatment Summary Form	Completion of treatment
Follow Up Form	3 months after end of SBRT
Tumor Response Form	Baseline, 3 months after end of SBRT
Progression Form	Time of disease progression
Death Form	Time of death

8.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 6.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

9.0 MEASUREMENT OF EFFECT

9.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response at 3 months post-completion of SBRT.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

RECIST evaluations will be performed by study physicians, not IRAC.

9.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since

they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

9.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT

scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in

ovarian cancer [JNCI 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

9.4 Response Criteria

9.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of

target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

9.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

9.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

9.4.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented

(taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

10.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least one patient has been enrolled) or one year after accrual has opened (if no patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

11.0 STATISTICAL CONSIDERATIONS

11.1 Stopping Criteria

If at any point in trial enrollment, >2 out of the first 5 patients experience symptoms of G3 or greater toxicity that is probably or definitely attributable to and did not pre-date SBRT, the trial will be suspended. Symptoms that pre-dated SBRT will not be count towards stopping criteria (example: central thorax patients requiring oxygen prior to and after SBRT will not be scored as G3 toxicity, however a new O2 requirement after RT would count towards stopping criteria). If at any time a grade 5 toxicity (death) is observed that is probably or definitely attributable to treatment, accrual will be suspended and the event will be reviewed by the principal investigator. Since some patients accruing to the trial may have metastatic disease, it is anticipated that deaths unrelated to the trial may be observed. Death that is felt either due to disease progression or patient comorbidity will not result in trial suspension.

11.2 Sample Size

The primary endpoint of this study is to assess the feasibility of surface-guided, respiratory gated delivery of CT-guided stereotactic radiotherapy for upper abdomen and lower thorax malignancies by confirming that gated treatment can be delivered successfully in more than 75% of scheduled treatment fractions using a novel surface guidance system. A total of 10 evaluable patients (as defined in Section 5.2) will be included, with five treatment fractions each, for a total of n = 50 evaluable fractions. In order to assess the feasibility of the gating methodology on the novel surface guidance system, we conducted a one-sample reliability demonstration test based on the binomial distribution. The study will be powered based on an expected success rate of 95% and a minimum accepted rate of 75%. With 10 patients and 5 fractions per patient, 50 total fractions (n=50) would be assessed. In-patient correlation is anticipated, as surface-guided delivery is in part patient-surface dependent, with an anticipated value of 0.2. With a one-sided alpha of 0.25 and n=50 fractions across 10 unique patients, we would have a minimum of 92% power to detect feasibility of successful gated delivery.

11.3 Primary Objective

Demonstrate that surface guided, respiratory gated delivery of CT-guided stereotactic adaptive radiotherapy (CT-STAR) is feasible in the abdomen and lower thorax by confirming that gated treatment can be delivered successfully in more than 75% of scheduled treatment fractions using a novel surface guidance system. Success will be defined as delivery of a given treatment fraction in one on-table attempt, without requiring use of a secondary (backup) motion management system, or alternative treatment machine. Unsuccessful delivery of a fraction will be defined as multiple attempts for gating without reproducible positioning, breath-hold, and/or surface guidance feedback, such that the fraction is abandoned.

11.4 Exploratory Objectives

- Determine geometric agreement between breath-hold positions as determined by a novel surface guidance system vs. concomitant breath-hold CBCT image sets. Geometric agreement will be evaluated by average symmetric surface distance (ASSD), modified Hausdorff distance (MHD), and Dice similarity coefficient measurements.
- Evaluate the compatibility of a standard-of-care respiratory gating system and the novel surface-guidance system for concomitant use. This will be evaluated qualitatively.
- Determine the minimum safe planning target volume (PTV) and planning organ-at-risk volumes (PRV) to be subsequently utilized with the novel surface guidance system. This will be determined through measurement evaluations in the first exploratory endpoint.
- Determine the local, in-field control rate at three months post-treatment. This will be determined by the treating physicians using RECIST criteria.
- Determine acute toxicity rates at three months post-treatment. This will be assessed by a qualitative description of grade 3 or higher non-hematologic toxicity events related to radiation therapy at three months post-treatment.
- Identify patient and or treatment factors that maximize the potential efficacy of surface guided breath-hold respiratory gating. These include factors such as surface topography features as well as skin tone. This will be evaluated qualitatively.

11.5 Statistical Analysis Plan

Our principal objective in this trial will be to determine the feasibility of surface guided, respiratory gated delivery of CT-guided stereotactic adaptive radiotherapy (CT-STAR) in the abdomen and lower thorax using a novel surface-guidance system. Given that no prior data exists for thoracic or abdominal SBRT using this surface guidance system for respiratory gating, we will also report descriptive statistics for treatment adaptation, dosimetry, geometric and phase agreement between the novel surface guidance system and CBCT, acute toxicity, in-field control rates, and minimum acceptable PTV and PRV expansions for treatment planning. As a pilot study we will establish these baseline parameters.

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APPENDIX A: Karnofsky Performance Scale

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

APPENDIX B: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event

- 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
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX C: Reporting Timelines

Expedited Reporting Timelines		
Event	**HRPO**	**QASMC**
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.	
Protocol exception	Approval must be obtained prior to implementing the change	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Breach of confidentiality	Within 10 working days.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

Routine Reporting Timelines		
Event	**HRPO**	**QASMC**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.
Minor deviation	Report summary information at the time of continuing review.	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days.	

Routine Reporting Timelines		
Event	**HRPO**	**QASMC**
	If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	