A Phase II Study of One Fraction Simulation-Free Treatment with CT-Guided Stereotactic Adaptive Radiotherapy for Patients with Oligometastatic and Primary Lung Tumors (ONE STOP)

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Protocol Revision History

Initial Approval Version	**03 January 2024**
Amendment #1 Version	**07 January 2025**

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:	A Phase II Study of One Fraction Simulation-Free Treatment with CT-Guided Stereotactic Adaptive Radiotherapy for Patients with Oligometastatic and Primary Lung Tumors (ONE STOP)
Study Description:	Stereotactic body radiotherapy (SBRT) has become a standard of care for medically inoperable or high-risk operable early-stage non-small cell lung cancer (NSCLC) patients. It is also increasingly used to treat lung metastases in patients with oligometastatic disease. While SBRT is a powerful tool for the treatment of lung tumors, access to specialized treatment can be limited for patients who live far away from a treatment center. Geographic accessibility can be limiting even for patients receiving one fraction lung SBRT, as the typical consult, CT simulation, and one-fraction treatment workflow is typically at least two to three weeks from start to finish, with a minimum of three in-person appointments. In this study, a high-quality cone beam CT (CBCT) on-board imaging platform (HyperSight; Varian Medical Systems, Palo Alto, CA) will be coupled with advanced motion management and treatment techniques as well as Ethos (Varian Medical Systems, Palo Alto, CA) daily online adaptation to simulation-free workflow for one fraction SBRT. This has the potential to reduce the time it takes a patient to be cured of their lung tumor from two to three weeks to two to three hours. In this novel workflow, patients will undergo telephone/online consent followed by a diagnostic scan-based pre-plan for one fraction SBRT. On the morning of treatment, a brief follow-up appointment will be followed by treatment on the HyperSight/Ethos platform. Patients will be treated using a simulation-free workflow. A HyperSight Thorax Slow protocol CBCT will be acquired for study purposes, and then the patient will be treated with online adaptive CBCT-guided radiotherapy on the Ethos/HyperSight platform. Treatment delivery will take place following contouring and treatment planning. Patients will undergo standard of care simulation imaging in parallel for comparison. The purpose of this study is to evaluate the feasibility of a ONE fraction Simulation-free Treatment with CT-guided stereotactic adaptive radiotherapy for Oligometastatic and Primary lung tumors (ONE STOP) workflow for patients with small, peripheral primary or oligometastatic lung tumors.
Objectives:	Primary Objective: To demonstrate the feasibility of the ONE STOP workflow for patients with small, peripheral primary or oligometastatic lung tumors.

	Exploratory Objectives: 1. To assess the time it takes to complete the ONE STOP workflow. 2. To assess patient satisfaction with the ONE STOP workflow. 3. To assess local control at the 3-month time point. 4. To assess toxicity at the 3-month time point. 5. To evaluate dosimetry-related factors of ONE STOP and how they compare to the standard-of-care one-fraction lung SBRT workflow. 6. To evaluate the quality of retrospectively reconstructed 4D-CBCT from the Thorax Slow scans acquired as a part of this study.
Endpoints:	Primary Endpoint: Feasibility is defined as the successful completion of the ONE STOP workflow through treatment delivery in at least 70% of patients. Successful completion of the workflow is defined as ONE STOP plan creation and delivery of the fraction using the study workflow in one on-table attempt. Unsuccessful completion of the workflow is defined as multiple attempts of the ONE STOP workflow for one patient without treatment delivery such that the study workflow is abandoned and a traditional one-, three-, or five-fraction plan is delivered. Exploratory Endpoints: 1. Total workflow time (from start of plan creation through end of treatment delivery). 2. Patient reported experience measures (PREMs). 3. Local control at 3-months as measured by RECIST criteria. 4. Toxicity at 3-months as measured by CTCAE v 5.0. 5. Dosimetry evaluation and comparison to the standard one-fraction SBRT workflow. 6. Retrospective thorax Slow and 4D-CBCT reconstruction evaluation.
Study Population:	This study will enroll 10 evaluable adult patients with small (< 5 cm), peripheral (≥ 2 cm from the proximal bronchial tree) histologically or radiographically diagnosed primary non-small cell lung cancers or oligometastatic cancers with lung tumors who are candidates for one fraction lung SBRT.
Phase:	II
Description of Sites / Facilities Enrolling:	This study will enroll patients at Siteman Cancer Center at Washington University School of Medicine.
Description of Study Intervention:	HyperSight is a novel on-board imaging platform equipped with rapid-acquisition high-quality CBCT imager capable of acquiring images sufficient for both simulation and treatment. Ethos is a unique ring-gantry CT-guided linear accelerator notable for having a

	dedicated artificial intelligence treatment planning system to allow for online adaptive radiotherapy. These platforms will be used to enable the ONE STOP workflow. In this study, consenting and eligible patients will receive a prescription dose of 25-34 Gy in one fraction with adaptation based on daily anatomic changes as per clinical standard of care.
Study Duration:	18 months (enrollment) + 1 day (treatment) + 3 months (follow-up) + 9 months (analysis)
Participant Duration:	3 months

1.0 BACKGROUND AND RATIONALE

1.1 Rationale for SBRT for lung tumors

Over the past two decades, stereotactic body radiotherapy (SBRT) has established itself as a definitive treatment for patients with inoperable or high-risk operable early-stage non-small cell lung cancer (NSCLC).[1,2] SBRT involves the focused delivery of multiple beams that converge on a single target to deliver an ablative dose of radiation therapy, typically in five or fewer treatments. SBRT is a highly effective therapy for early-stage lung cancer that is well tolerated by patients and minimizes overall treatment time with low toxicity rates. Three-year local control rates for early-stage NSCLC treated with SBRT have been reported to be 85% or higher in several series.[3–5] More recently, emerging data suggests that SBRT may also be a reasonable therapy for patients with medically operable disease who prefer non-surgical management.[2,6–8]

SBRT also has an established role in the treatment of oligometastatic lung disease.[9–11] In the past decade or so, the management of oligometastatic disease, typically defined as one to five metastatic lesions or sites, has changed dramatically as it has become apparent that aggressive local treatment can prevent patients from resuming systemic therapy or changing systemic therapy, and can even prolong progression-free and overall survival. Several randomized trials have demonstrated the benefit of SBRT for oligometastatic cancers, and these trials demonstrated that the ablation of oligometastatic lung disease is safe and efficacious.

1.2 Rationale for one fraction SBRT

While lung SBRT is most commonly delivered in three or five fractions, one fraction SBRT is an emerging treatment paradigm. In the definitive setting for primary lung cancer, a phase II randomized trial (RTOG 0915) compared single fraction (34 Gy) vs multi-fraction (48 Gy in 4 fractions) SBRT for patients with small (< 5 cm) early-stage NSCLC and demonstrated similar toxicity, local control, and overall survival in each arm.[12] In the oligometastatic setting, the phase II randomized trial SAFRON II compared single fraction (28 Gy) vs multi-fraction (48 Gy in 4 fractions) lung SBRT for patients with oligometastatic lung disease.[13] Similar to RTOG 0915, SAFRON II demonstrated comparable toxicity, local control, and overall survival in each arm.

The emphasis on SBRT in the radiation oncology community has arisen in part as an improvement in patient convenience and access to care. Reducing traditional conventional treatment times from three to six weeks of treatment down to one week simplifies treatment for patients who live far from a treatment center or who are unable to take off extended time from work. However, while SBRT is a powerful tool for the treatment of lung tumors, even with one week of treatment, access to specialized SBRT can be limited for patients who live far away from a treatment center. It has been demonstrated that increased geographic accessibility to oncology centers is correlated with improved disease outcomes, and patients who live farther away from a treatment center (e.g. > 50 miles) are less likely to receive advanced oncologic therapies.[14,15] Therefore, reducing treatment time to one

fraction represents a necessary step towards increasing access to lung SBRT for our most geographically limited patients.

1.3 Rationale for a simulation-free workflow

While one fraction SBRT promises to improve access to patient care, the standard workflow can still be challenging for patients to complete. The standard one fraction lung SBRT workflow is still fairly demanding, as the typical consult, CT simulation, and one-fraction treatment paradigm is typically at least two to three weeks from start to finish, with a minimum of three in-person appointments. To further improve access to lung SBRT, there is sufficient rationale to consider a one-day, one-visit workflow with a diagnostic-scan based pre-plan (simulation-free) to further simplify the process patients.

Diagnostic scan-based planning has become increasingly popular, as several studies have demonstrated feasibility of this paradigm with comparable plan quality between the simulation-free workflows and the standard CT-simulation workflows.[16,17] A simulation-free workflow has also proven feasible to be combined with adaptive radiotherapy for patients with bone metastases.[18] While not simulation-free, a same-day "one-stop-shop" single fraction lung SBRT workflow has been demonstrated on an MRI-guided platform on a small patient population (N = 10) which had high patient satisfaction.[19] Limiting the entire workflow to one machine is critical for patients with limited geographic accessibility, as CT simulation appointments can be challenging to obtain in a high-volume clinic.

1.4 Rationale for the utilization of the Varian HyperSight on-board imaging platform

Varian Medical System Inc. (Siemens Healthineers, Palo Alto, CA) recently developed the HyperSight radiotherapy system, which combines a linear accelerator with a novel CBCT imaging platform. This new imaging platform consists of an O-shaped gantry treatment device combined with a high-speed CBCT system that has been FDA approved for simulation and treatment. The HyperSight imaging platform features a larger detector, allowing the use of a full-fan x-ray beam configuration resulting in decreased image acquisition time (6 seconds). The platform also includes improved detector efficiency that produces lower beam noise. Finally, the new source and detector has decreased computed tomography dose indices (CTDI), which is a standardized measure of radiation dose output of a CT scanner so that radiation exposure can be compared between devices/machines. The HyperSight CTDI values show a reduction of over 50% compared to the current exposure rates from on-board imaging with head and body phantoms.

The HyperSight platform represents an ideal machine for the ONE STOP workflow. The high quality CBCT imager will enable simulation-free treatment, with an adapted plan generated all while the patient is on the treatment table. The HyperSight is equipped with a breath-hold image protocol for tumor delineation and a slow (> 1 min) free-breathing protocol to acquire a 4D average image on which the actual treatment plan will be created. While the HyperSight does not currently have 4D image capabilities (which are generally performed as a part of lung SBRT simulation to assess tumor motion), we will use the slow

free-breathing images from this study to develop and evaluate a 4D-CBCT reconstruction methodology for the HyperSight platform. In the interim, all patients will undergo a 4D-CT simulation independent of ONE STOP workflow to confirm patient's tumor motion is within limits of what can be safely treated with the slow free-breathing scan.

1.5 Rationale for online adaptive radiotherapy

When delivering one fraction of definitive lung SBRT, precision is key. One method to improve precision is through online adaptive radiotherapy (ART). In ART, real-time adjustments are made to a radiation therapy plan daily in accordance with variation in the patient's anatomy while the patient is on the treatment table. The Department of Radiation Oncology at Washington University/Siteman Cancer Center was the first to clinically implement online ART for SBRT utilizing magnetic resonance imaging (MRI) guided radiotherapy (also known as SMART).[20–22] Utilizing this workflow, the treating radiation oncologist is able to adjust a radiotherapy plan daily to account for inter-fraction motion and/or day-to-day anatomic variation, allowing for dose escalation while minimizing toxicity through maximizing the dosimetric therapeutic index. The dosimetric benefits of online ART have also been demonstrated in thoracic disease, specifically with regards to central and ultra-central tumors. Our department has recently established the feasibility of CT-guided stereotactic ART (also known as CT-STAR) for ultra-central thoracic disease, and a phase I trial in this patient population is underway.

While patients intended to be treated with one fraction lung SBRT typically have peripheral tumors which stray far from critical OARs, in the ONE STOP setting the use of ART may account for small changes in patient rotation and position which become more critical when delivering one-fraction SBRT compared to multi-fraction SBRT. In this light, ART may increase the precision of the delivery of one-fraction SBRT and therefore the ONE STOP workflow. Furthermore, the ART technique and the ability to adapt the patient's plan to their anatomy at time of treatment makes diagnostic-scan based planning, and skipping traditional CT-simulation, feasible in order to shorten and simplify the workflow from the patient perspective.

1.6 Rationale for utilization of the Varian Ethos system

Varina Medical Systems has created a commercial CT-guided radiotherapy machine capable of online ART (Ethos). This unique, ring-gantry CT-guided linear accelerator is notable for having a dedicated artificial-intelligence (AI) driven treatment planning system (TPS) to allow for streamlined online ART workflows. The original iteration of this machine had a high-quality CBCT system—but not of high-enough quality to permit simulation imaging acquisition. However, our department has upgraded the Ethos linear accelerator with the HyperSight imaging platform, enabling a union of machinery that is ideal for the testing of the ONE STOP workflow as it combines CBCT imaging sufficient for simulation-free treatment and an integrated TPS capable of ART.

1.5 Study rationale

In this study, we aim to leverage HyperSight's high-quality cone beam CT (CBCT), coupled with advanced motion management and treatment techniques as well as Ethos daily online adaptation, to create a simulation-free treatment workflow for one fraction SBRT. This has the potential to reduce the time it takes a patient to be cured of their lung tumor from two to three weeks to two to three hours. In this novel workflow, patients will undergo a telephone/online consent and, once they've demonstrated interest in participating in the trial, a diagnostic-scan based pre-plan will be created. On the morning of treatment, a formal consult appointment will be followed by treatment on the HyperSight/Ethos platform. A HyperSight Thorax Slow protocol CBCT will be obtained for treatment planning purposes, and then the patient will be treated with online adaptive CBCT-guided radiotherapy on the Ethos/HyperSight platform. Following contouring and treatment planning, we will proceed with treatment delivery. Patients will undergo standard of care simulation imaging in parallel for comparison. A 4D-CBCT reconstruction methodology (Zhang, Med Phys, 2022) using a slow (1 minute) HyperSight scan will be retrospectively evaluated and validated after treatment completion. We propose to evaluate the feasibility and safety of the ONE STOP workflow for patients with small, peripheral primary or oligometastatic lung tumors with feasibility defined as successful completion of the ONE STOP workflow through treatment delivery in at least 70% of patients.

1.6 Risk/Benefit Assessment

1.6.1 Known Potential Risks

The treatment of small, peripheral lung tumors with one-fraction SBRT is associated with high local control rates and limited toxicity. Ablative radiotherapy to the thorax in general may be associated with pneumonitis, chest wall/rib pain, esophagitis, and fatigue. While these toxicities should not be understated, there is no reason that toxicity should be different from historical controls on this study.

1.6.2 Known Potential Benefits

Access to advanced medical care is challenging for patients with limited accessibility, and even the standard SBRT workflow (which typically spans several weeks and several in-person appointments) can be challenging for patients who have limited resources or who are unable to take extended time off of work. Therefore, a workflow such as ONE STOP which has the potential to reduce the in-person commitment for curative lung SBRT from several weeks and several appointments to a few hours on one day may provide increased access to lung SBRT for some of our most resource challenged patients. Furthermore, as patients will undergo a screening 4D-CT simulation appointment, patients in whom the workflow is not feasible or who screen fail out of the study will already have the requisite imaging to complete the standard lung SBRT workflow with limited additional time burden due to the study.

1.6.3 Assessment of Potential Risks and Benefits

Given the above potential risks and benefits, we believe that the benefits of performing a feasibility study for the ONE STOP workflow for patients with oligometastatic and primary lung tumors outweigh the risks. We will adhere to standard one-fraction lung SBRT constraints and so efficacy and toxicity will be within the standard of care, and the patients will undergo standard treatment planning simultaneously, which will allow patients in whom the workflow is not feasible or who screen fail to be treated off trial without a significant increase in time burden for the patient.

2.0 OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**	**Justification for Endpoints**
Primary		
To demonstrate the feasibility of the ONE STOP workflow for patients with small, peripheral primary or oligometastatic lung tumors.	Feasibility is defined as the successful completion of the ONE STOP workflow through treatment delivery in at least 70% of patients. Successful completion of the workflow is defined as ONE STOP plan creation and delivery of the fraction using the study workflow in one on-table attempt. Unsuccessful completion of the workflow is defined as multiple attempts of the ONE STOP workflow for one patient without treatment delivery such that the study workflow is abandoned and a traditional one-, three-, or five-fraction plan is delivered.	As this is a novel workflow and the treatment itself is standard of care with well established efficacy and toxicity outcomes, the primary endpoint of this study is feasibility of this novel workflow as defined by successful completion of the workflow in at least 70% of patients. The efficacy and toxicity of the treatment itself is not in question as the doses delivered with this novel workflow are standard of care.
Exploratory		
1. To assess the time it takes to complete the ONE STOP workflow.	Total workflow time (from start of plan creation through end of treatment delivery).	The goal of this novel workflow is to complete the entire day of treatment workflow in as minimal time as possible, therefore necessitating total

		workflow time as a necessary endpoint.
2. To assess patient satisfaction with the ONE STOP workflow.	Patient reported experience measures (PREMs).	This is a novel workflow which may be of interest for patients traveling from far away, and therefore patient satisfaction with the workflow will be on interest.
3. To assess local control at the 3-month time point.	Local control at 3-months as measured by RECIST criteria.	The radiation dose is standard of care and so efficacy should be within historical expectations. 3-month RECIST will be to confirm there were not any acute deviations from expectations.
4. To assess toxicity at the 3-month time point.	Toxicity at 3-months as measured by CTCAE v 5.0.	The radiation dose is standard of care and so toxicity should be within historical expectations. 3-month toxicity assessment will be to confirm there were not any acute deviations from expectations.
5. To evaluate dosimetry-related factors of ONE STOP and how they compare to the standard-of-care one-fraction lung SBRT workflow.	Dosimetry evaluation and comparison to the standard one-fraction SBRT workflow.	This is a novel workflow which has not yet been clinically implemented and so dosimetry evaluation and comparison to standard workflow will be used to confirm the novel workflow is dosimetrically consistent with the standard workflow.
6. To evaluate the quality of retrospectively reconstructed 4D-CBCT from the Thorax Slow scans acquired as a part of this study.	Retrospective thorax Slow and 4D-CBCT reconstruction evaluation.	We plan of evaluating the HyperSite thorax Slow protocol so see if this can serve as a surrogate for intra-fraction motion management in future studies/treatment.s

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. One of the following diagnoses:
   a. Histologically or radiographically diagnosed stage I-IIA (AJCC, 8th ed.) non-small cell lung cancer .
      i. Clinical AJCC stage I defined as stage 1A1 (T1a1N0M0, T1a tumor less than or equal to 1 cm), stage 1A2 (T1bN0M0, T1b tumor between 1 and 2 cm), and stage 1A3 (T1cN0M0, T1c tumor between 2 and 3 cm).
      ii. Clinical AJCC stage IB defined as T2aN0M0, T2a tumor between 3 and 4 cm.
      iii. Clinical AJCC stage IIA defined as T2bN0M0, T2b tumor between 4 and 5 cm.
   b. Oligometastatic lung tumor secondary to a primary cancer of any type/histology. Oligometastatic patients may include patients with:
      i. 1-5 sites of metastatic disease with at least one lung lesion intended to be treated with SBRT
      ii. More than 5 sites of metastatic disease with oligo-progressive disease in the lung intended to be treated with SBRT.

2. Lesions must be small and peripheral.
   a. Small is defined as max tumor dimension of 5 cm or less.
   b. Peripheral is defined as greater than 2 cm from the proximal bronchial tree/mediastinum.

3. Tumors and anatomy amenable to one-fraction lung SBRT confirmed by meeting of one-fraction lung SBRT target and constraint metrics on a diagnostic-scan based preplan.
   a. Patients who do not meet this criterion will be screen fails and triaged to the standard lung SBRT workflow and treated off trial.

4. Lesions must have a maximum superior to inferior motion of 1 cm on 4D-CT imaging.
   a. Patients who do not meet this criteria will be screen fails and triaged to the standard lung SBRT workflow and treated off trial.

5. At least 18 years of age.

6. Able to understand and willing to sign an IRB approved written informed consent.

3.2 Exclusion Criteria

1. Past history of radiotherapy within the projected treatment field of any of the disease sites to be treated by ONE STOP SBRT.

2. Pregnant and/or breastfeeding. Patient must have a negative pregnancy test within 14

days of ONE STOP SBRT.

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 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 Database

All patients must be registered through the Siteman Cancer Center 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).

4.5 Strategies for Recruitment and Retention

All attending physicians, clinical residents, physicists, and nurses in the radiation oncology department will be educated on this protocol in order to be aware of the relevant inclusion and exclusion criteria. Furthermore, the clinical research team will perform outreach to the greater thoracic multi-disciplinary team including medical oncologists and thoracic surgeons to educate them on the protocol and the patient population the protocol applies to in order to help drive recruitment.

5.0 TREATMENT PLANNING AND DELIVERY

5.1 Radiation Therapy Workflow Guidelines

5.1.1 Telephone/online consent

The entirety of the ONE-STOP workflow can be reviewed in Figure 1. Patient candidates will be screened by the study team and potential candidates will undergo either a telephone/online consent or an onsite consult with written consent no more than 30 days prior to their day of treatment. Telephone/online consent will be performed using a REDCap online consent mechanism in with consent will be obtained on an online form using an e-signature. For patients who undergo telephone consent, they will need to have a formal consult visit the day of their treatment prior to initiating the treatment workflow.

If a patient consents via the REDCap mechanism, the treatment tea will need to place a note in Epic with at least one sentence descripting the patient's diagnosis and treatment plan for insurance authorization purposes.

Given that the ultimate goal of this protocol is to evaluate the feasibility of the ONE STOP simulation free SBRT workflow, and not necessarily the feasibility telephone consents, patients who are seen for onsite consultations priorm to screening are also eligible.

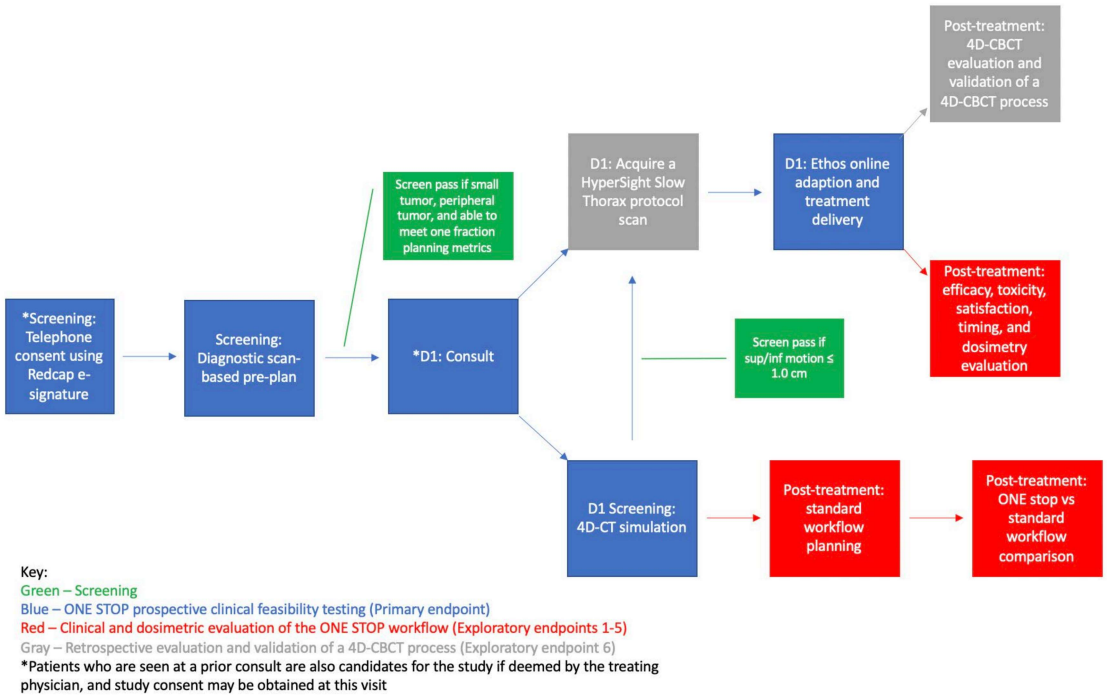

Figure 1. ONE STOP workflow

5.1.2 Diagnostic-scan based pre-plan

Following consent, a diagnostic scan-based pre-plan will be created for the patient. This pre-plan will be a one-fraction SBRT plan with the intended recommended prescription dose created on a diagnostic image (diagnostic chest CT or the CT component of a diagnostic PET/CT) by the study medical physicist or dosimetrist. As the Ethos TPS will auto-segment all OAR contours in the pre-planning and planning process, the only physician contours required for this stage of the protocol will be the gross tumor volume (GTV) and the planning target volume (PTV; 5 mm volumetric expansion). This plan will be required to meet standard institutional one-fraction lung SBRT constraints (Table 1). If these constraints are unable to be met on this pre-plan, the patient will be treated with the standard lung SBRT workflow off-trial. The pre-plan must be approved by the treating physician.

Organ at Risk	**Constraint metric**
Stomach	D 5 CC < 17.4 Gy
Stomach	D 0.03 CC < 22.0 Gy
Brachial plexus	D 3 CC < 13.6 Gy
Brachial plexus	D 0.03 CC < 16.4 Gy
Esophagus	D 5 CC < 11.9 Gy
Esophagus	D 0.03 CC < 15.4 Gy
Spinal cord	D 1.2 CC < 8 Gy
Spinal cord	D 0.35 CC < 10 Gy
Spinal cord	D 0.03 CC < 14 Gy
Chest wall	D 0.03 CC < 33 Gy

Chest wall	D 0.03 CC < 105% Rx
PTV	V 100% Rx > 95%
PTV	V 95% Rx = 100%
Lungs – GTV	CV 7 Gy [CC] > 1500 CC
Lungs – GTV	V 8 Gy < 37% Rx
Skin	D 10 CC < 25.5 Gy
Skin	D 0.03 CC < 27.5 Gy
Trachea	D 4 CC < 17.4 Gy
Trachea	D 0.03 CC < 20.2 Gy
Bronchus	D 4 CC < 17.4 Gy
Bronchus	D 0.03 CC < 20.2 Gy
Liver	CV 11 Gy [CC} > 700 CC
Great vessels	D 10 CC < 31 Gy
Great vessels	D 0.03 CC < 37 Gy
Heart	D 15 CC < 16 Gy
Heart	D 0.03 CC < 22 Gy
Chest wall	D 5 CC < 28 Gy

Table 1.

5.1.3 Day of treatment consult visit

On the day of treatment, patients who underwent a telephone/online consent will undergo a consult visit during which they will be evaluated by the treating physician. At this time, they will be asked to sign standard consent forms.

For patients who were consented after a prior consult visit for treatment for their present lung tumor, they do not need to undergo a day of treatment consult or follow-up visit.

5.1.4 Dose, Fractionation

Radiotherapy will consist of one-fraction SBRT using the Ethos linear accelerator and online adaptive treatment planning system. Patients will be treated with a dose ranging from 25 to 34 Gy in one fraction as delineated by the treating radiation oncologist. This range extends up to the standard definitive dose for primary lung tumors (34 Gy) and down to a dose safe to deliver to metastatic patients receiving concurrent immunotherapy (25 Gy). Of note, safety of treatment will be kept within established guidelines based on standard institutional constraints applied to normal tissues. Patients will be planned for an intended dose of 25-34 Gy to the PTV.

5.1.5 Simulation Procedures/Patient Positioning

Prior to treatment, the patient will undergo standard of care 4D-CT simulation on a conventional CT scanner. This screening simulation will be used to evaluate patient tumor motion. If maximum tumor motion is discovered to be greater than 1 cm (even with the presence of abdominal compression) in any direction, the patient

will be considered inevaluable and treated with standard of care SBRT using the 4D-CT simulation scan obtained. Therefore, the screening 4D-CT also acts as a failsafe for patients on study, as in the instance that the ONE STOP workflow can not be completed or tumor motion is too great for treatment on study, the screening 4D-CT can be used for off study treatment planning, allowing for no delay in patient care compared to our institutional standard of care. If the tumor motion is 1 cm or less in the superior/inferior dimension, the patient will proceed with ONE STOP workflow and the 4D-CT simulation images will be used for study purposes.

Next, patients will be moved to the treatment room and a slow free-breathing CBCT (HyperSight Slow Thorax protocol) on the HyperSight scanner will be acquired which will be used for treatment planning and study purposes. At this point, the treatment process will be initiated on the HyperSight/Ethos platform. A dedicated immobilization system used for SBRT lung treatments with patient specific molding will be used. Patients will be positioned such that both arms are overhead or with the ipsilateral arm up and the contralateral arm down. Intravenous and oral contrast will not be used per standard peripheral lung SBRT protocol. Patients may be treated free-breathing or at end-exhale breath-hold per Section 5.1.6.

Patients with inadequate tumor visualization at HyperSight simulation (as determined by the treating physician and physicist) will be considered a process failure and the workflow will be considered infeasible for that patient.

The treatment workflow will be performed online (while the patient is on the treatment table).

5.1.6 Internal Target Volume (ITV), Clinical Target Volume (CTV) and Planning Target Volume (PTV) Definitions

The treatment target will be defined based on the gross tumor volume (GTV) as visualized on the Thorax Slow scan. No CTV expansion will be utilized, as per standard-of-care procedures in the setting of lung SBRT. As the Thorax Slow GTV (iGTV) is an estimate of motion, it will in part serve as the estimation of the ITV. The PTV expansion will be generated off of the iGTV and will reflect standard lung SBRT uncertainty as well as uncertainty between the equivalency of the iGTV and a standard 4D-CT derived ITV, which will be estimated by our physics team.

5.1.7 Organ at Risk (OAR) Definition

Minimum required OARs to be delineated (naming convention in parentheses) for the purposes of this study will include the heart (Heart), esophagus (Esophagus), left lung (Lung_L), right lung (Lung_R), bilateral lungs (Lungs), lungs minus GTV (Lungs-GTV), great vessels (Great vessels), brachial plexus (Brachial plexus), spinal cord (Spinal cord), trachea (Trachea), chest wall (Chestwall) and proximal bronchial tree (Bronchial tree), presuming these OARs are in the intended treatment field. These OARs will be auto-segmented by the Ethos TPS and edited by the

treating physician, physicist, and Advanced Practicing Radiation Therapist. The OARs may be delineated by the treating radiation oncologist and/or dosimetrist. Additional OARs may be delineated at the discretion of the treating radiation oncologist.

5.1.8 Initial Treatment Planning

All patients will be initially planned to 25-34 Gy to the PTV. This will be subject to standard of care one-fraction SBRT constraints. Dose volume histogram (DVH) information for the target volumes and surrounding critical structures is mandatory. This is to assist in interpreting outcome, including morbidity. The coverage goal to the PTV will be for 95% of the volume to be receiving 100% of the prescription. Volumetric modulated arc therapy (VMAT) limiting entrance through the contralateral lung will be used for treatment.

5.1.9 SBRT Dose Constraints

Standard institutional one fraction dosimetric objectives (Table 1) for the thorax will be used.

5.1.10 Adaptive Treatment Planning

Once the online adaptive treatment process has been initiated, a Thorax Slow CBCT will be acquired on which the original plan will be overlaid and adapted. The adaptive physician will confirm target alignment, via rigid propagation, and make any adjustments to the target contour if needed. The iGTV should reflect the gross tumor as depicted on the Slow Thorax scan obtained for adaptive treatment planning. All OARs within the 3 cm Ethos contour ring as well as any relevant OARs as dictated by the treating physician and physicist will be re-contoured per standard institutional practice. An online adaptive plan will then be generated by the treatment planning system. The adapted treatment plan will always be selected for treatment unless the adapted plan results in a dosimetric variation deemed clinically unacceptable by the treating radiation oncologist or physicist. The adapted plan must be approved by the treating physician prior to QA and delivery of treatment to the patient.

5.1.11 Quality Assurance of Adaptive Plans

Patient specific calculation-based QA will be performed at each fraction prior to delivery of the adaptive treatment plan. 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, evaluating the dose volume histograms and 3D gamma analysis of all voxels within the patient. After completion of the automated checks, a final review and sign-off by the adaptive physicist will be required prior to proceeding to treatment delivery. Off-

line, post-treatment measurement based QA will be performed as well.

5.1.12 Intrafraction Motion Management

At time of HyperSight 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. The reference surface will be monitored using the Identify system and a respiratory trace will be generated and displayed to the treatment team for respiratory gating of treatment delivery. The gating window will encompass the entire breathing pattern and image and treatment will be gated if the patient moves or takes in a deeper breath than their baseline respiratory signal. After treatment adaptation, a repeat will be obtained to evaluate for any patient motion during the adaptive planning process. Shifts can be applied as needed prior to initiation of delivery. At least one intra-fraction CBCT will be taken, mid-treatment, e.g., after each arc in VMAT plans, and at the end of treatment delivery.

5.1.13 Post ONE-STOP SBRT dosimetry evaluation

ONE STOP dosimetry will be evaluated post-ONE STOP SBRT in order to compare plan quality between the diagnostic-scan based pre-plan, standard workflow 4D-CT simulation plan, and the on-table adaptive plan. We will also compare methods of motion assessment and management via the acquired HyperSight simulation CBCT free-breathing and breath-hold scans.

We will also use the free-breathing HyperSight Thorax Slow protocol images to validate a 4D-CBCT reconstruction methodology which has already been described (Zhang, Med Phys, 2022) and to develop a tool to use this 4D-CBCT methodology to assess motion for inclusion within online adaptive radiation. We will directly compare motion assessment from the 4D-CBCT with that from the standard workflow 4D-CT simulation images.

5.2 Definitions of Evaluability

Endpoint	**In order to be evaluable for this endpoint, a patient must have…**
Primary: Feasibility	Started the ONE STOP workflow (plan creation and treatment delivery).
Exploratory: Total workflow time	Completed the ONE STOP workflow
Exploratory: PREMs	Completed the ONE STOP workflow and the PREMs
Exploratory: Local control at 3 months by RECIST	Completed the ONE STOP workflow and had a post-treatment disease assessment
Exploratory: Toxicity at 3 months by CTCAE v 3.0	Completed the ONE STOP workflow

Exploratory: Dosimetry evaluation and comparison	Completed the ONE STOP workflow
Exploratory: Retrospective thorax Slow and 4D-CBCT reconstruction evaluation	Completed the ONE STOP workflow

Note that patients whose maximum tumor motion (during the screening simulation) is discovered to be greater than 1 cm (even with the presence of abdominal compression) in any direction will be considered inevaluable.

5.3 Concomitant Therapy and Supportive Care Guidelines

Patients are permitted to receive systemic therapy while intended to and being treated with ONE STOP SBRT. Dose adjustments from 34 Gy down to 25 Gy are allowed on this study in order to allow for the delivery of a safe dose of ablative radiotherapy concurrently with systemic therapy.

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.

5.5 Duration of Therapy

Treatment consists of a single fraction of SBRT.

5.6 Duration of Follow-up

Patients will be followed for three months following the completion of ONE STOP 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 and evaluation of toxicity. 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 their three-month follow-up appointment.

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 one month 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 DOSE DELAYS/DOSE MODIFICATIONS

Dose modifications are permissible as long as the intended PTV dose is within the described 25-34 Gy range. Treatment delays are acceptable as long as the patient's treatment course is contained within two weeks from initial date of intended treatment.

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix A for definitions.

Adverse events will be tracked from start of treatment through 3 months after completion 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

Refer to the data submission schedule in Section 9 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 7.1.

7.1 WU PI Reporting Requirements

7.1.1 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.

7.1.2 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. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

7.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 7.1 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.

8.0 STUDY CALENDAR

	Pre-Screening	Screening	Pre-treatment	D1	3-months post-ONE STOP SBRT
Informed consent		X			
Medical history / physical exam[3]		X			
FDG-PET/CT and/or CT chest (with or without contrast)[4]		X			X
Diagnostic scan-based pre-plan	X				
Pregnancy test [1]			X		
ONE STOP SBRT				X	
Workflow feasibility assessment				X	
AE assessment				X	X
PREMs[2]				X	
RECIST		X			X

1. Women of childbearing potential only
2. Refer to Appendix C
3. May be done up to 30 days prior to registration
4. May be done up to 60 days prior to registration

9.0 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
Treatment Summary Form (includes PREMs and Workflow Feasibility data)	End of treatment
Toxicity Form	Continuous
Follow Up Form	Month 3
RECIST Form	Baseline, Month 3

9.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 7.0) 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.

10.0 MEASUREMENT OF EFFECT

10.1 Antitumor Effect

For the purposes of this study, patients should be re-evaluated for response at three 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 are used in the RECIST criteria.

10.2 Disease Parameters

Target lesions: Target lesions will be biopsy proven stage I-IIA non-small cell lung cancers which are visible on CT imaging and amenable to treatment with SBRT per the treating radiation oncologist. Target lesions may also include non-biopsied lesions which

have radiographic characteristics of non-small cell lung cancer and have been deemed radiographically diagnosed non-small cell lung cancer by the treating radiation oncologist.

Target lesions will be central or ultra-central in location as defined as follows. Central lesions are defined as lesions 1 cm or less from the trachea, carina, main bronchi, bronchus intermedius, or lobar bronchi. Ultra-central lesions are defined as lesions touching the trachea, carina, main bronchi, bronchus intermedius, or lobar bronchi. They will be classified as either central or ultra-central tumors prior to start of therapy.

10.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 60 days before the beginning of the treatment. Measurements recorded prior to therapy will include the maximum diameter of a tumor as well as distance from the proximal edge of the tumor (in relation to the bronchial tree) to the bronchial tree. Ultra-central lesions will be measured as 0 cm from the bronchial tree.

Additional measurements to be recorded prior to treatment but that do not require the use of a ruler may include GTV volume and PTV volume, amongst others.

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.

The following imaging modalities may be utilized for target delineation and characterization.

Conventional CT: 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.

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.

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.

10.4 Response Criteria

10.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of target lesion.

Partial Response (PR): At least a 30% decrease in the sum of the diameter of the target lesion, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameter of the target lesion, 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 progression).

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

10.4.2 Duration of Response

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

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.

11.0 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 five patients have been enrolled) or one year after accrual has opened (if fewer than five 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 and accrual by cohort (central thorax, liver, and non-liver abdomen)
- 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 separated by cohort
- 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.

12.0 STATISTICAL CONSIDERATIONS

12.1 Definition of Primary Endpoint

Feasibility. Feasibility will be defined as successful completion of the ONE STOP workflow through treatment delivery in at least 70% of patients.

Successful completion of the workflow will be defined as ONE STOP plan creation and delivery of the fraction using the study workflow in one on-table attempt. Unsuccessful completion of the workflow will be defined as multiple attempts of the ONE STOP workflow for one patient without treatment delivery such that the study workflow is abandoned and a traditional one, three, or five fraction plan is delivered. Reasons for unsuccessful completion of the ONE STOP workflow may include inadequate tumor visualization on the HyperSight platform, machine breakdown or malfunction during treatment, or patient unable to tolerate the time on table needed to complete the on table workflow. Additional reasons for incomplete delivery may be designated by the study and treatment team including the treating physician, treating physicist, study physicians, and study physicists.

12.2 Definition of Exploratory Endpoints

Total workflow time. This will be calculated as time from patient walk-IN to HyperSight/Ethos vault to time of patient walk-OUT of HyperSight/Ethos vault (Appendix B).

Patient satisfaction. This will evaluated using patient reported experience measures (PREMs, Appendix C) on the day of treatment.

Local control. This will be evaluated at baseline and at 3-months using response assessment via the RECIST criteria (see section 10.4).

Toxicity. This will be evaluated one day of treatment and at 3-months using adverse events (AE) assessments.

Dosimetry evaluation. ONE STOP dosimetry will be evaluated with a goal of comparing plan quality between the diagnostic-scan based pre-plan, standard workflow 4D-CT simulation plan, HyperSight adapted plan, and the on-table adaptive plan. We will also compare methods of motion assessment and management to evaluate the 4D-CBCT, Thorax Slow protocol, and breath-hold images.

Retrospective 4D-CBCT reconstruction evaluation. The Thorax Slow protocol images will be used to develop and validate a 4D-CBCT reconstruction methodology for HyperSight and to develop a tool to use this 4D-CBCT methodology to assess motion for inclusion within online adaptive radiation. We will directly compare motion assessment from the 4D-CBCT with that from the standard workflow 4D-CT simulation images.

12.3 Sample Size

The primary endpoint of this study is to determine the feasibility of ONE STOP one-fraction SBRT for patients with small, peripheral primary or oligometastatic lung tumors. Ten evaluable patients will be enrolled in this feasibility study.

Feasibility of the workflow will be defined as delivery of the treatment fraction at time of the first on-table treatment attempt in at least 70% of patients. If we can successfully deliver the treatment fraction at time of the first on-table treatment attempt in 70% of patients, while maintaining the safety and efficacy profile of standard one-fraction SBRT, we will consider this study as having provided sufficient pilot data to support more widespread study of the ONE STOP paradigm. Success will be defined as ONE STOP plan creation and delivery of the fraction using the study workflow in one on-table attempt. Unsuccessful planning and workflow delivery will be defined as multiple attempts of the ONE STOP workflow for one patient without treatment delivery such that the study workflow is abandoned and a traditional one, three, or five fraction plan is delivered.

12.4 Statistical Analysis Plan

The long-term goals of this study will be to improve patient outcomes and care by reducing time to treatment, through the ONE STOP expedited radiotherapy delivery workflow. Thus, our primary endpoint of feasibility here will be characterized using descriptive statistics.

For the dosimetry exploratory endpoints, one-way ANOVA, or non-parametric equivalents (i.e., KruskalWallis test) if the data are not normally distributed, will be conducted to compare plan quality between the diagnostic-based plans, on-table adaptive plans, and traditional simulation-based plans. The remaining exploratory endpoints will be described using descriptive statistics.

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APPENDIX A: 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 B: Workflow timing form

Patient: _____ **Date:** _____

DOB: _____

Patient walk-IN time: _____ **Patient walk-OUT time:** _____

Time for patient set-up and obtaining CBCT:

Start time: _____ End time: _____ Total: ____ minutes

Time for ETHOS adapted plan generation and evaluation (time from influence generation to selection of plan for treatment):

Start time: _____ End time: _____ Total: ____ minutes

Time for dose prediction and plan evaluation/optimization:

Start time: _____ End time: _____ Total: ____ minutes

Time for treatment (patient alignment/shifts, intra-fraction motion management, MU delivery):

Start time: _____ End time: _____ Total: ____ minutes

Shifts (mm): Vert: _____ Long: _____ Lat: _____

Time for QA/physics signoff:

Start time: _____ End time: _____ Total: _____ minutes

Workflow completed and treatment delivered:

Yes: _____ No: _____

Name and title of person recording: _____

APPENDIX C: Patient reported experience measures form

Patient reports (1) not at all satisfied, (2) slightly satisfied, (3) moderately satisfied, or (4) very satisfied for the following procedures:

Interval consult to treatment start _____

Treatment start to treatment completion _____

Treatment duration _____

Overall satisfaction with workflow _____

APPENDIX D: Study-Specific DSM Tables

Protocol Objectives and Subject Evaluability	
Objective	**# of patients evaluable for this endpoint to date**
Primary	
To demonstrate the feasibility of the ONE STOP workflow for patients with small, peripheral primary or oligometastatic lung tumors.	
Exploratory	
To assess the time it takes to complete the ONE STOP workflow	
To assess patient satisfaction with the ONE STOP workflow	
To assess local control at the 3-month time point	
To assess toxicity at the 3-month time point	
To evaluate dosimetry-related factors of ONE STOP and how they compare to the standard-of-care one-fraction lung SBRT workflow	
To evaluate the quality of retrospectively reconstructed 4D-CBCT from the Thorax Slow scans acquired as a part of this study	

Interim Analysis and Early Stopping Rules
Does the study design include an interim toxicity analysis? No
Does the study design include an interim futility analysis? No
Are there early stopping rules that outline circumstances under which the study must be suspended or closed? No

Feasibility and Response				
UPN	**Treatment date**	**ONE STOP workflow successfully completed? (y/n)**	**Local control at 3 mos**	**Patient replaced?**