Title: Pilot Study of Same-session MR-only Simulation and Treatment with MRI-guided Adaptive Palliative Radiotherapy

NCT: NCT03824366

Version Date: 01/25/19

Pilot Study of Same-session MR-only Simulation and Treatment with MRI-guided Adaptive Palliative Radiotherapy

Washington University School of Medicine
Department of Radiation Oncology
660 South Euclid Avenue, Campus Box 8224
St. Louis, MO 63110

Protocol #: Pending
Version Date: 01/25/19

Principal Investigator: **Hyun Kim, M.D.**
Phone: (314) 362-8502
E-mail: kim.hyun@wustl.edu

Sub-Investigators: Soumon Rudra, M.D.
Lauren Henke, M.D., MSCI
Olga Green, Ph.D.

Clinical Trials.gov #: Pending

Pilot Study of Same-session MR-only Simulation and Treatment with Stereotactic MRI-guided Adaptive Palliative Radiotherapy

Protocol Revision History

Initial Approval Version	**mm/dd/yyyy**
Amendment #1 Version	**mm/dd/yyyy**

Table of Contents

1 BACKGROUND

1.1 Palliative Radiotherapy

Palliation of symptoms from metastatic cancer can be achieved by delivery of radiation therapy (RT)[1]. Emergent conditions with established evidence for palliative RT include critical cancer-induced symptoms such as hemoptysis[2,3], gastrointestinal (GI) bleeding[4,5], pelvic bleeding[6–9], bulky mediastinal disease causing airway or vascular compression, and superior vena cava (SVC) syndrome[2,10]. Painful bony metastases may also require short courses of radiation to palliate symptoms that are refractory to narcotics. Oncology patients with these conditions frequently require inpatient hospitalization. They may have limited treatment options, given that such syndromes often indicate large burden of metastatic disease and/or disease progression despite prior therapies. In this setting, RT can palliate symptoms and potentially mitigate life threatening symptoms with minimal risk for toxicity.

1.2 EBRT for Palliation

External beam RT (EBRT) has long been the approach of choice for such palliative treatments. The traditional workflow for a patient to receive palliative radiation using EBRT requires multiple steps including consultation with a radiation oncologist, computed tomography (CT) simulation for radiation therapy planning, quality assurance of the planned radiation course, and final approval of the plan by the radiation oncology physician. Given these numerous important steps, multiple delays in the treatment planning workflow can occur and result in delays to start of RT for patients requiring urgent therapy.

At our clinic, the scarcity of available appointment times for CT simulation would result in delay of RT planning and delivery. Since delays are unacceptable in treating urgent cases, these patients may start RT without simulation, using simplified radiation planning performed with manual calculations for the first one or two fractions of treatment, while an opening in the CT simulation schedule is pending. These “clinical set-ups” consume significant time from the treatment team and result in both dose uncertainty and workflow inefficiency. Even when CT simulation is successfully performed for patients requiring urgent palliative RT, delivery of treatment using conventional linear accelerators may be limited with regards to imaging guidance for treatment setup accuracy. On board imaging for linear accelerators are limited to two-dimensional portal films or three-dimensional cone beam CTs both of which have difficulty in discriminating various soft tissue densities.

The combination of clinical set-ups with lack of CT simulation data and poor soft-tissue resolution with on board imaging leads to use of larger treatment volumes to address spatial uncertainty, as well as dose uncertainty from manual calculations. This subsequently increases risk of toxicity. This is especially significant if upfront palliative doses are to be followed by definitive treatment doses. Clearly, there is a need for improvement in the radiation therapy workflow and image guidance for treatment delivery in patients who require urgent palliative RT.

1.3 MRgRT for Palliation

A solution may exist with the use of magnetic resonance image-guided radiotherapy (MRgRT). MRgRT involves RT delivery using an integrated MRI, radiotherapy device, and dedicated treatment planning system. MRI-guidance is performed with a 0.35 Tesla imaging unit while treatment is delivered through an integrated Cobalt-60 radiotherapy device or linear accelerator (LINAC). Imaging with MRgRT can be performed daily, using a 17 second or 172 second volumetric scan, with excellent soft-tissue contrast that is sufficient for real-time treatment planning and plan modification while the patient lies on the treatment table[11,12]. These daily treatment plans, typically created in response to changes in daily anatomy, are termed "adaptive radiotherapy" (ART). The MRI-guided ART treatment planning process includes nearly all components of traditional treatment planning for palliative RT, such as volumetric imaging, target volume delineation by the physician, treatment plan generation, and quality assurance with an independent, Monte Carlo-based dose verification[11,13].

However, the traditional treatment planning workflow for MRgRT is limited by the current need for pre-treatment MRI and CT simulation imaging, which provide data to select appropriate beam geometry and electron density information for dose calculation. The standard of care for electron density calculation is a CT scan of the patient in the treatment position and immobilization device that will be used for daily treatments. An ideal workflow for urgent palliative MRgRT would permit use of same session-MR imaging to generate a treatment plan while the patient is on the treatment table. In most instances, conventional urgent palliative RT plans use simple radiation beam arrangements and large field sizes to ensure target coverage. The traditional field arrangements are anterior-posterior (AP) and posterior-anterior (PA) beam pairs, regardless of tumor site, which may treat large amounts of normal tissue. Use of pre-specified beam angles would mitigate the need for pre-treatment imaging to define beam geometry and improve the feasibility of creating the clinical plan in a time frame that is acceptable and tolerable for the patient to remain on the treatment table. Further, MRgRT allows real-time gating of tumor motion, so a significantly smaller amount of normal tissue would be treated by using MRgRT.

Regarding CT-free treatment planning for MRgRT, some progress has been made towards this goal at other institutions. Investigators at the University of Wisconsin have used their MRgRT device for same-session simulation and treatment planning and delivery of the first fraction of 2D and 3D-conformal palliative spine radiation treatments. However, following the first treatment fraction, patients then underwent traditional CT simulation and treatment planning for treatment plan and dose verification; ART was used only to expedite the first fraction.

In such treatment planning, bulk density overrides have been used to assign electron densities based on typical values for basic tissue types (bone, fat, lung, soft tissue)[14]. Bulk density overrides are an FDA-approved mechanism for dose extrapolation in MRgRT radiation planning, and can overcome the absence of CT density information[15]. Such overrides carry an anticipated dose uncertainty of <3%, which is considered acceptable especially in the setting of urgent palliative treatments[16]. For comparison, manual

calculations of dose such as those used in clinical setups rely only upon measurement of the patient width in the treatment plane (the patient "separation"), without correction for heterogeneity of internal structure composition. This approach, although frequently utilized in the first one to two fractions for urgent treatments, results in an average single-fraction dose discrepancy between manually and computer-calculated dose of up to 10%, with uncertainty up to 25-30% for sites like the thorax where tissue density heterogeneity is substantial[17,18]. Although this uncertainty is then averaged out over the remaining treatment fractions following CT-simulation, the uncertainty of MR-only dose calculation using bulk density override may indeed be an improvement upon the cumulative dose uncertainty of a treatment course utilizing manual calculations for one or more treatment fractions. Additionally, the < 3% dose uncertainty incurred using bulk density override for MR-only planning is well within the AAPM Task Group 141 recommendation of ± 5% cumulative dose uncertainty[19].

1.4 Rationale

Given the availability of MRgRT technology and the growing clinical experience with MR-only planning, we propose to evaluate the feasibility of same-session MR-only simulation and treatment with urgent palliative RT for patients with diagnosis of metastatic malignancy presenting with hemoptysis, GI bleeding, pelvic bleeding and bulky mediastinal disease/SVC syndrome. Although MRgRT has been used for palliative spine treatments previously at our institution, this expedited same-session MR-only simulation and treatment will include non-spine treatments. This proposed study is unique in that patients will not undergo CT simulation at any point during their treatment course and will instead have same-session MR-only simulation and treatment planning, on-table, using the ART workflow. In this manner, patients requiring urgent treatment could initiate treatment as early as the day of initial radiation oncology consultation.

2 OBJECTIVES

2.1 Primary Objective

Demonstrate feasibility of same-session MRI-only simulation and treatment with MRI-guided palliative radiation therapy for hemoptysis, GI bleeding, pelvic bleeding, and SVC syndrome/ bulky mediastinal disease. Feasibility will be defined as more than 70% of patients receiving at least 70% of their scheduled treatment fractions on the first on-table attempt for each respective fraction.

2.2 Exploratory Objectives

1. Determine the proportion of patients who complete planned course of palliative radiation therapy.
2. Determine the on-table time required for each component of same-session MRI-only simulation and treatment with plan generation for the initial treatment fraction and for subsequent treatment fractions.

3 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

1. Diagnosis of malignancy (biopsy proven or high clinical suspicion with urgent/emergent clinical indications for palliative RT)
2. Requires delivery of palliative radiation therapy for the treatment of painful metastasis, hemoptysis, gastrointestinal bleeding, pelvic bleeding, or superior vena cava syndrome/bulky mediastinal disease.
3. Has had or will have a diagnostic CT for the region being treated.
4. At least 18 years of age.
5. Able to understand and willing to sign an IRB-approved written informed consent document.

3.2 Exclusion Criteria

1. Pregnant. Patients of childbearing potential must have a negative pregnancy test within 14 days of study entry.
2. Medical contraindication to undergoing MR imaging.

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 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 have 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.

5 RADIATION THERAPY GUIDELINES

5.1 Dose, Fractionation

Radiation therapy dose and fractionation will be one of the following standard regimens:

- 8 Gy in 1 fraction
- 20 Gy in 5 fractions
- 30 Gy in 10 fractions
- 25 Gy in 5 fractions
- 37.5 Gy in 15 fractions

Due to the palliative nature of treatments, radiation prescriptions may vary from single fraction regimens to fifteen fraction regimens.

5.2 Patient Positioning

All patients will undergo volumetric MR imaging on treatment days in positioning appropriate for the specific treatment site. This will most frequently be supine with arms positioned so not in the way of treatment beams.

5.3 Definitions

5.3.1 Gross Tumor Volume (GTV)

The GTV will be defined as the visible gross tumor on the volumetric MR imaging obtained on the first day of treatment.

5.3.2 Clinical Target Volume (CTV)

The treating physician may choose to define a CTV based on clinical judgement (margin that accounts for microscopic disease), but this is not required.

5.3.3 Planning Target Volume (PTV)

If a CTV is created, the PTV is defined as a volumetric 5 to 10 mm margin expansion of the CTV (to account for setup error). If no CTV is created, the PTV is defined as a volumetric 5 to 20 mm margin expansion of the GTV.

5.4 Same-session MR-only Simulation and Fraction 1 Treatment Planning

All patients will need to be screened with an MR screening questionnaire with clearance by MR level II staff prior to MR imaging. Prescription dose per fraction will be chosen from the above doses at the discretion of the treating physician. The protocol will not require segmentation of critical structures given the relatively low doses used during palliative radiation therapy. Coverage goal for the PTV will be for 95% of the volume to be covered by 95% of the dose.

On the day of Fraction 1, each patient will be planned based on their MRI volumetric image set obtained during simulation. A bulk density override method will be used to manually assign relative electron density values to the MRI dataset for the purpose of dose calculation. Initial plan parameters may be generated based on diagnostic imaging. For example, voxels representing the patient's bones will be assigned an average bone density, voxels representing fat will have a different density assignment, etc. On subsequent treatment fractions, another volumetric MRI image will be obtained on the treatment machine itself, and the plan will be adjusted based on anatomy and patient habitus of the day. Previously assigned density values will be reviewed and adjusted if needed, after which the final clinical treatment plan will be created.

5.5 Quality Assurance of the Daily Treatment Plan

Patient specific QA will be performed at each fraction prior to delivery of the treatment plan. Given that dose measurements will not be possible with the patient on the table, this will be achieved by performing an independent Monte Carlo dose calculation on the image of the day, using the exported beam parameters, and mapped electron density. The independently calculated dose distribution will be compared to the dose distribution exported from the MRgRT system, looking at dose volume histograms and 3D gamma analysis of all voxels within the patient. In addition, in-house plan integrity verification software will be utilized to evaluate plan quality and integrity via plan parameters including contours, beam angles, segments, and monitor units. After completion of the automated checks, a final review by physics will be required prior to proceeding to treatment delivery.

5.6 Follow Up

Patients will be assessed once per week in routine on treatment visits to assess for acute toxicity. All patients will undergo routine clinical follow-up with no protocol-required follow-up studies after radiation therapy is complete.

6 REGULATORY AND REPORTING REQUIREMENTS

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

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 6.2.

6.1 Definitions

6.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

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

6.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

6.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

6.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

6.1.5 Unanticipated Problems

Definition:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

6.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB

6.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm

6.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

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

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

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event

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

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (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 a QASMC auditor.

6.4 Timeframe for Reporting Required Events

Adverse events captured in the CRFs will be tracked for 1 week following the last day of MRgRT. For the purposes of this protocol, reportable adverse events are toxicities that did not predate MRgRT and are probably or definitely attributable to protocol procedures.

7 STUDY CALENDAR

	Screening	MRI-guided Radiation Therapy
Informed consent	X	
Medical history	X	
MRI-Screening Questionnaire	X	
Pregnancy test[1]	X	
Volumetric MRI		X
AE assessment		X

1. Women of childbearing potential only

8 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	Prior to starting treatment
Treatment Summary Form	Completion of last fraction of MRgRT
Toxicity Form Follow-up Form	Continuously through 1 week after last treatment
Death Form	1 week after last treatment (if applicable)

9 DATA SAFETY AND 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.
- 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 with the number of dose-limiting toxicities indicated.
- 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.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Calculations

Given this is a pilot study to demonstrate feasibility, clinical considerations instead of power calculations were used to determine sample size. The primary objective will be to report feasibility of same-session MRI-only simulation and treatment with MRI-guided palliative radiation therapy for painful metastasis, hemoptysis, GI bleeding, pelvic bleeding, and SVC syndrome/ bulky mediastinal disease. The goal accrual will be 20 patients. We are interested in precise estimates of feasibility of the proposed treatment plan, as well as outcome variability that will aid in the planning of a larger, sufficiently powered efficacy trial. A sample size of 20 will allow us to be relatively precise in our conclusions regarding feasibility outcomes. For example, if we observe an 80% feasibility rate (i.e. 16 patients out of the 20 enrolled in the study receiving at least 70% of their scheduled treatment fraction for each respective fraction), the 95% CI for that rate would be (62.5% - 97.5%). Similarly, the secondary objectives do not require power calculations.

10.2 Stopping Criteria

If at any point in trial enrollment, >2 out of the first 5 patients, or >4 out of the first 10 patients are unable to complete the first fraction of treatment, the trial will be suspended.

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 patients accruing to the trial have metastatic disease, it is anticipated that deaths unrelated to the trial may be observed. Death that is felt to be either due to disease progression or patient comorbidity will not be scored as grade 5 toxicity and will not result in trial suspension.

10.3 Statistical Analysis Plan

Patient baseline characteristics will be presented as mean and standard deviation or count and percentage. Overall feasibility will be reported as the number of patients receiving at least 70% of their scheduled treatment fraction for each respective fraction with percentage in all patients recruited, and a 95% confidence interval will be generated. Feasibility will be defined as 70% of patients receiving at least 70% of their scheduled treatment fraction. Second, fraction plans will be divided by median fraction used into two groups, low fraction group and high fraction group. Median feasibility and range will be described for each group, and a Wilcoxon rank-sum test will be used to compare the feasibility among the two different fraction groups.

11 REFERENCES

1. Lutz ST, Jones J, Chow E. Role of radiation therapy in palliative care of the patient with cancer. *J Clin Oncol*. 2014. doi:10.1200/JCO.2014.55.1143
2. Rodrigues G, Videtic GMM, Sur R, et al. Palliative thoracic radiotherapy in lung cancer: An American Society for Radiation Oncology evidence-based clinical practice guideline. *Pract Radiat Oncol*. 2011. doi:10.1016/j.prro.2011.01.005
3. Langendijk J a, ten Velde GP, Aaronson NK, de Jong JM, Muller MJ, Wouters EF. Quality of life after palliative radiotherapy in non-small cell lung cancer: a prospective study. *Int J Radiat Oncol Biol Phys*. 2000.
4. Kim MM, Rana V, Janjan NA, et al. Clinical benefit of palliative radiation therapy in advanced gastric cancer. *Acta Oncol*. 2008. doi:10.1080/02841860701621233
5. Tey J, Back MF, Shakespeare TP, et al. The role of palliative radiation therapy in symptomatic locally advanced gastric cancer. *Int J Radiat Oncol Biol Phys*. 2007. doi:10.1016/j.ijrobp.2006.08.070
6. Biswal BM, Lal P, Rath GK, Mohanti BK. Hemostatic radiotherapy in carcinoma of the uterine cervix. *Int J Gynaecol Obstet*. 1995. doi:002072929502454K [pii]
7. Halle JS, Rosenman JG, Varia MA, Fowler WC, Walton LA, Currie JL. 1000 CGY single dose palliation for advanced carcinoma of the cervix or endometrium. *Int J Radiat Oncol Biol Phys*. 1986. doi:10.1016/0360-3016(86)90130-6
8. Hodson DI, Krepart G V. Once-monthly radiotherapy for the palliation of pelvic gynecological malignancy. *Gynecol Oncol*. 1983. doi:10.1016/0090-8258(83)90016-1
9. Duchesne GM, Bolger JJ, Griffiths GO, et al. A randomized trial of hypofractionated schedules of palliative radiotherapy in the management of bladder carcinoma: results of medical research council trial BA09. *Int J Radiat Oncol Biol Phys*. 2000. doi:10.1016/S0360-3016(00)00430-2
10. Stevens R, Macbeth F, Toy E, Coles B, Lester JF. Palliative radiotherapy regimens for patients with thoracic symptoms from non-small cell lung cancer. *Cochrane Database Syst Rev*. 2015;1(1469-493X (Electronic)):CD002143. doi:10.1002/14651858.CD002143.pub4.www.cochranelibrary.com
11. Acharya S, Fischer-Valuck BW, Kashani R, et al. Online Magnetic Resonance Image Guided Adaptive Radiation Therapy: First Clinical Applications. *Int J Radiat Oncol Biol Phys*. 2016;94(2):394-403. doi:10.1016/j.ijrobp.2015.10.015
12. Noel CE, Parikh PJ, Spencer CR, et al. Comparison of onboard low-field magnetic resonance imaging versus onboard computed tomography for anatomy visualization in radiotherapy. *Acta Oncol (Madr)*. 2015;54(9):1474-1482. doi:10.3109/0284186X.2015.1062541
13. Henke L, Kashani R, Robinson C, et al. Phase I trial of stereotactic MR-guided online adaptive radiation therapy (SMART) for the treatment of oligometastatic or unresectable primary malignancies of the abdomen. *Radiother Oncol*. 2017;xxx. doi:10.1016/j.radonc.2017.11.032
14. De Costa AMA, Mittauer KE, Ko HC, et al. Rapid Access Palliative Radiation Workflow Using MRI-Guided Single-Session Simulation, Online Adaptation, and Treatment. *Int J Radiat Oncol • Biol • Phys*. 2017;99(2):S126. doi:10.1016/j.ijrobp.2017.06.295
15. Karotki A, Mah K, Meijer G, Meltsner M. Comparison of bulk electron density and voxel-

based electron density treatment planning. *J Appl Clin Med Phys*. 2011. doi:10.1120/jacmp.v12i4.3522
16. Jonsson JH, Karlsson MG, Karlsson M, Nyholm T. Treatment planning using MRI data: an analysis of the dose calculation accuracy for different treatment regions. *Radiat Oncol*. 2010. doi:10.1186/1748-717X-5-62
17. Van Dyk J, Keane TJ, Rider WD. Lung density as measured by computerized tomography: implications for radiotherapy. *Int J Radiat Oncol Biol Phys*. 1982. doi:10.1016/0360-3016(82)90587-9
18. Sontag MR, Battista JJ, Bronskill MJ, Cunningham JR. Implications of Computed Tomography for Inhomogeneity Corrections in Photon Beam Dose Calculations 1. *Radiology*. 1977. doi:10.1148/124.1.143
19. Stern RL, Heaton R, Fraser MW, et al. Verification of monitor unit calculations for non-IMRT clinical radiotherapy: Report of AAPM Task Group 114. *Med Phys*. 2011. doi:10.1118/1.3521473