Phase IA/IB Trial of Real-time MRI-Guided Stereotactic Body Radiation Therapy and Microwave Ablation for Non-Operable Renal Cell Carcinoma

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SYNOPSIS:

Title	Real-time MRI-Guided Stereotactic Body Radiation Therapy and Microwave Ablation for Non-Operable Renal Cell Carcinoma
Short Title	Microwave ablation with MRI-Guided SBRT Boost in Renal Cell Carcinoma
Protocol Number/ Date	UW15103
Study Duration	5 years
Study Center(s)	University of Wisconsin Hospital and Clinics Carbone Cancer Center, Madison, WI
Objectives	**Primary Objective(s):** The primary objective of this study is to determine the maximum tolerated dose (MTD) of stereotactic body radiation therapy followed by microwave ablation for non-operable renal cell carcinoma. **Secondary Objective(s):** The secondary objectives of this study include estimation of rates of local control, progression-free survival, overall survival, and tumor response on biopsy.
Number of Subjects	Based on the 3+3 dose-escalation design, between 9-18 patients will be enrolled in the initial Phase IA study, with an optional 10 patients enrolled on a Phase IB expansion cohort.
Inclusion Criteria	1. Histologically confirmed diagnosis of renal cell carcinoma 2. Tumor size >4cm in largest dimension 3. ECOG performance status of < 2 4. Age > 18 years 5. Signed informed consent document(s) 6. Patients with metastatic disease will not be excluded
Treatment summary	The proposed study would be performed as a 3+3 dose-escalation study wherein three dose levels of SBRT would be evaluated: 1. Dose level I: 6 Gy x 5 fractions 2. Dose level II: 8 Gy x 5 fractions 3. Dose level III: 10 Gy x 5 fractions Radiation treatments will be delivered two to three times a week, with five fractions completed over two weeks. Four to six weeks after radiation treatment, patients will undergo repeat CT or MRI imaging to assess tumor response and suitability for microwave ablation. Eight weeks after the conclusion of SBRT, patients will undergo microwave ablation (approximately 12 weeks after registration).

SCHEMA

Phase I: Microwave ablation with MRI-Guided SBRT Boost in Renal Cell Carcinoma

Informed Consent

Registration in study, if eligibility criteria satisfied

SBRT (week 1 and 2)

Dose-escalation levels (for Phase IA):

- Dose level I: 6 Gy x 5 fractions
- Dose level II: 8 Gy x 5 fractions
- Dose level III: 10 Gy x 5 fractions

Dose-level for Phase IB will be based on the MTD from Phase IA

Four weeks after SBRT completion: Assessment for ablation

Microwave ablation 8 weeks
from the completion of SBRT

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1. Protocol Summary

Renal cell carcinoma is traditionally managed via a surgical approach. Increasingly, local therapy with radiofrequency and microwave ablation is being utilized as an alternative for patients who may not tolerate a nephrectomy or who refuse one. Although local control rates for small lesions are excellent, they drop off precipitously for lesions over 4 cm. Furthermore, lesions in critical areas such as the renal hilum may be difficult to treat with this method. Stereotactic body radiation therapy (SBRT) has had a long record of treating patients with inoperable tumors in locations such as the lung and central nervous system, and there is increasing evidence that it may be useful for patients with renal cell carcinoma. The recent emergence of MRI-guided radiation therapy allows for direct visualization of tumors during treatment, and may potentially allow clinicians to treat tumors more precisely. This phase I study will treat renal cell carcinoma patients using a combination of MRI-guided stereotactic body radiation therapy and microwave ablation.

The specific aims of this study are:

1. To determine the safety and feasibility of treating patients with a combination of MRI-guided stereotactic body radiation therapy and microwave ablation.
2. To assess short and long-term toxicity rates of patients treated with a combined modality approach.
3. To assess local control, survival, and pathologic response to treatment

2. Introduction

The traditional management of renal cell carcinoma (RCC) has been total or partial nephrectomy. This has been shown to prevent long-term renal failure and cardiovascular disease, as well as decrease overall mortality[1]. Cytoreductive treatment has even been found to improve overall survival in the metastatic setting[2,3]. With the increasing numbers of renal masses found incidentally on routine imaging, focal therapies are being increasingly utilized as an alternative to partial nephrectomy for carefully selected patients who might not tolerate a nephrectomy or who refuse one. Studies of radiofrequency ablative treatments have reported disease-free survival, overall survival, and cause-specific survival rates of 83.1-97%, 63-97.8%, and 96.4-100%, respectively[4]. More recently, microwave ablation has emerged as an alternative to radiofrequency ablation with promising early results[5,6]. Although thermal ablative strategies may be comparable to partial nephrectomy especially when balanced against the potential morbidity of surgery, they are less effective at controlling larger tumors. Three centimeters has emerged as a common threshold above which thermal ablative strategies are less commonly recommended, with 5-year disease-free survival decreasing from 96% to 79%[7]. Microwave ablation is effective to 4cm; as with RFA, however, local control rates drop precipitously for tumors above 4cm[8].

The role of external beam radiation therapy in the treatment of RCC is less established, as it is typically considered a radioresistant entity. Radiation therapy is usually given in 30 or more doses of 2 Gy per fraction, delivered daily over several weeks. Stereotactic body radiation therapy (SBRT) differs from conventionally fractionated treatment, using radiation doses of up to 34 Gy in a single fraction. It is believed that at such high doses, radiation therapy is ablative[9]. Advances in physics, imaging, and motion management have made such treatment possible and it is considered standard of care in

medically inoperable non-small cell lung cancer [10]. Phase I studies utilizing SBRT in the treatment of renal cell carcinoma show promising results[11,12].

One challenge that exists when utilizing high doses of radiation therapy in the kidney is that of respiratory induced tumor motion. Respiratory gating techniques are utilized to minimize normal tissue irradiation. Nevertheless, any such technique is limited by the fact that it depends on the assumption that there is a good correlation between respiratory motion and tumor motion.

The recent emergence of a radiation treatment system allowing real-time MRI imaging during treatment may obviate the dependence on respiratory gating techniques[13]. Tracking tumor motion in real time allows the potential for the delivery of safe and effective radiation treatment with the goal of improving control rates of ablative treatments for large, medically inoperable renal cell carcinomas.

We propose a Phase I study to determine the feasibility of adding SBRT treatment for patients undergoing treatment for RCC. We hope to show that such treatment is feasible and safe.

3. Study Objectives

3.1 Working hypothesis – We hypothesize that the addition of SBRT treatment to microwave ablation is safe and can be delivered without undue toxicity.

3.2 Primary Objective - The primary objective of this study is to determine the maximum tolerated dose (MTD) of stereotactic body radiation therapy followed by microwave ablation for non-operable renal cell carcinoma. Toxicity will be evaluated via the CTCAE Criteria v5.0. Expected side effects of radiation treatment include potential fatigue, dermatitis, chest wall pain, nausea, and hematuria. Side effects of ablation may include hemorrhage, treatment site pain, urinary retention, and a decrease in glomerular filtration rate.

3.3 Secondary Objective - The secondary objectives of this study include estimation of rates of local control, progression-free survival, overall survival, and tumor response on biopsy.

3.4 Exploratory Objective – To assess pathologic response after stereotactic body radiation therapy and immune cell infiltrate.

3.5 Study Duration – We estimate that approximately 40-50 potentially eligible patients are seen at UWCCC each year. With a 3+3 study design and an estimated 20% rate of enrollment, we estimate it will take 1-2 years for patient accrual, treatment, and followup for determination of acute toxicity of the initial 9-18 patient Phase IA cohort. This cohort will then be followed for a period of 3 years, giving an estimated study duration of 5 years.

4. Selection of Patients

4.1 Inclusion Criteria
4.1.1 Patients with imaging findings consistent with renal cell carcinoma
4.1.2 Deemed medically inoperable per urology evaluation
4.1.3 Tumor size > 4cm in largest dimension

4.1.4 ECOG performance status of < 2
4.1.5 Age > 18 years
4.1.6 Signed informed consent document(s)
4.1.7 Patients with metastatic disease will not be excluded

4.2 Exclusion Criteria
4.2.1 Patients who fail MRI screening
4.2.2 Pregnant or nursing women
4.2.3 History of prior radiation therapy to the upper abdomen
4.2.4 History of invasive cancer in the last 3 years (except for appropriately treated low-risk prostate cancer, treated non-melanoma/melanoma skin cancer, appropriately treated ductal carcinoma in situ or early stage invasive carcinoma of breast and appropriately treated in-situ/early stage cervical/endometrial cancer)
4.2.5 Treatment with a non-approved or investigational drug within 28 days of study treatment

5. Registration Procedures

Patients may not begin protocol treatment prior to registration. All patients must meet eligibility criteria listed in Section 4 and provide written informed consent. The study coordinator will verify eligibility, assign a case number, and register the patient in the UWCCC ONCORE database prior to study treatment. The following information will be recorded:

5.1 Protocol number
5.2 Patient's name and initials
5.3 Patient's medical record number
5.4 Patient demographic data including gender, birth date, race and zip code.
5.5 Signed patient consent form dates
5.6 Attending physician
5.7 HIPAA authorization form dates

6. Treatment Plan/Overview

6.1 Overview

Patients will be referred to the study by their treating urologist. The urologist will determine the appropriateness for patient referral and discuss the option of study participation with their patients. After biopsy, patients will be treated on study with a course of SBRT treatment by a radiation oncologist. A 3+3 dose escalation scheme will be used. Four to six weeks after treatment, patients will be evaluated for microwave ablation by the treating radiologist with repeat imaging to ensure microwave ablation remains feasible. Two months after treatment, patients will be referred to an interventional radiologist for treatment with microwave ablation as well as repeat biopsy for exploratory analysis. Both SBRT and MWA will be administered on an outpatient basis. Details of treatment are as described below.

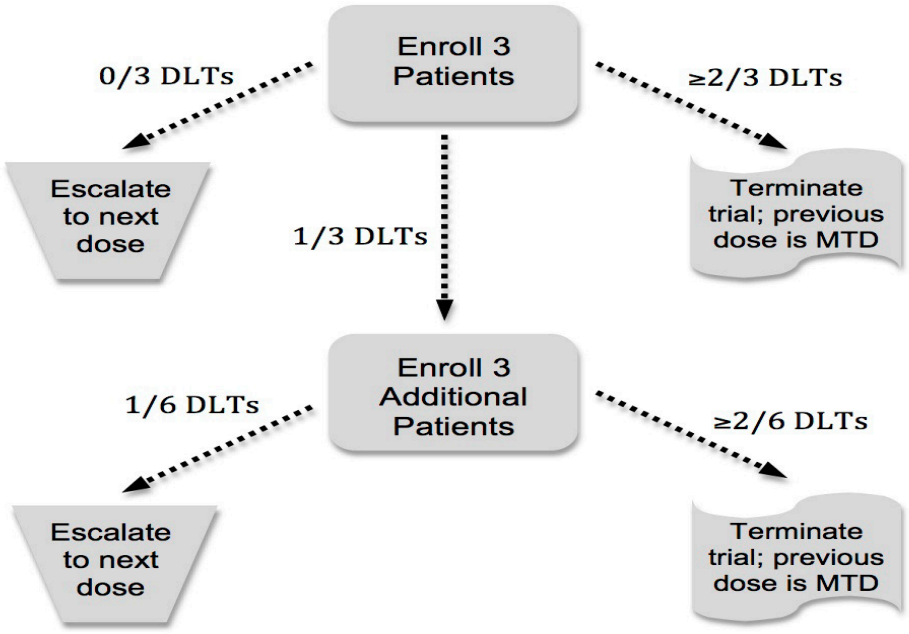
6.2 Dose escalation

6.2.1. The proposed study will follow a phase IA-B dose-escalation design wherein three SBRT dose levels targeting the primary tumor will be evaluated; level I: 6 Gy x 5 fractions (a common palliative dose), level II: 8 Gy x 5 fractions and level III: 10 Gy x 5 fractions (a common definitive dose).

6.2.2. Dose-limiting toxicity (DLT) will be defined as any grade 4 or higher toxicity that occurs within 30 days post MWA (approximately 90 days post SBRT) specifically: hemorrhage, hematoma, nephrotoxicity, gastric, duodenal or small bowel perforation or obstruction attributable to the radiation, the MWA or the combination of the treatment. Attributable DLT will be defined as that which is possibly, probably or definitely felt to be due to either radiation or ablation and occurring within the vicinity of the radiation treatment field (as reviewed by Drs. Bassetti/Wojcieszynski) or in the vicinity of the microwave ablation (as reviewed by Dr. Lee). Grade 3 toxicity is not considered a DLT as it may be seen in routine, standard of care treatment. If progressive disease is found at the time of interval imaging and the patient is deemed ineligibile for MWA, the patient will not be part of the cohort used for DLT analysis as his/her inclusion may falsely lower potential toxicity rates.

6.2.3. A standard, traditional 3+3 design will be utilized for dose escalation (Figure). For each three patient cohort, DLT will be assessed. In the case of 0/3 DLTs, the dose will be escalated to the next level. In the case of 2/3 DLTs, the dose escalation will be halted with the previous level being the MTD. In the case of 1/3 DLTs, an additional three patients will be enrolled at the current dose level. If no additional DLTs are seen, the dose will be escalated to the next level. In the event of a total of 2 or more DLTs in 6 patients, the dose escalation will be halted with the previous dose level being the MTD. Once the MTD has been established, the MTD will be used for the subsequent Phase IB expansion cohort.

6.2.4. Dose escalation/de-escalation will continue until a maximum of 18 patients are accrued or dose-level I is shown to exceed the MTD. To allow efficient conduct of the study without compromising patient safety, accrual in the phase-IA study will be done in groups of three patients, with subsequent dose level accrual only after the occurrence of DLT thirty days after ablation has been evaluated for all at the curret dose level. The phase-IB portion of the trial will consist of an additional ten patients (for a theoretical maximum of 28 total patients) to validate the results of phase-IA and provide a preliminary assessment of efficacy.



6.3 Pretreatment workup

6.3.1. CT/MRI scan of the chest, abdomen, and pelvis
6.3.2. Laboratory evaluation including complete blood count (CBC) with differential, basic metabolic panel (BMP) including creatinine
6.3.3. A renal nuclear medicine scan may be obtained prior to radiation treatment or microwave ablation to estimate functional renal parenchymal volume if deemed necessary by the treating physicians.

6.4 Radiotherapy details

6.4.1. Simulation

All patients will be planned using MRI simulation on the MRIdian system (Viewray Inc., Mountain View, CA). Simulation scans will be performed with patients supine in the arms up or down position. MRI coils will be placed directly on the patient. Patients will be simulated with a breath hold technique. A standard-of-care computed-tomography (CT) planning scan will be obtained in the same position as the MRI planning scan in order to obtain density data for dose calculations. The MRI and CT planning scan will then be imported in to the Treatment Planning System (TPS) (Viewray Inc., Mountain View, CA) which will then be utilized to create SBRT treatment plans.

6.4.2. Target Delineation

Gross tumor volume (GTV) will be contoured with the help of co-registered pretreatment imaging. No expansion to a clinical tumor volume (CTV) will be performed. A planning tumor volume (PTV) will be customized for each patient at the time of simulation to account

for each patient's ability to breath-hold, reproducible tumor motion, and estimated variation in daily setup.

6.4.3. Radiation Dose

The PTV will be treated to a dose of 6, 8, or 10 Gy for 5 fractions, for a total dose of 30, 40, and 50 Gy, respectively as per current dose cohort.

6.4.4. Radiation fractionation

Radiation treatments will be delivered on alternate days. Treatments will preferentially start on Mondays, although the start of therapy on Tuesday or Wednesday is also acceptable.

6.4.5. SBRT Planning Process

An inverse IMRT planning process will be performed using the treatment planning system to determine if the desired PTV dose is feasible to administer without exceeding a safe radiation dose to normal structures.

6.4.6. Normal Tissue Constraints

No volume outside of the PTV should receive more than 105% of the prescription dose. Planning dose-volume constraints (Table 1) are based on constraints used by Hong et al.[14] as well as Pham et al[12]. If dose constraints are unable to be met for a given patient at the current dose level, the dose per fraction will be decreased until acceptable constraints are met and the patient will continue off study. Of note, no specific dose constraints will be utilized for the involved kidney. This has been most extensively studied in a series of patients who underwent SBRT to a solitary kidney, with no reports of late toxicity noted[15]. As a result, the QUANTEC group guidelines recommend no specific dose constraints be applied to the involved kidney during SBRT[16].

Structure	Dose Constraint
Spinal Cord	Dmax = 25 Gy
Stomach	D0.1cc < 32 Gy
Bowel	D0.1cc < 32 Gy
Liver	D700cc < 15 Gy
Contralateral Kidney	V13 < 30%, Mean < 10 Gy

Table 1: SBRT Dose Constraint Table

6.5 Microwave ablation (MWA)details

All procedures will be performed under sedation utilizing ultrasound and computed tomography (CT) guidance for percutaneous antenna placement and confirmation. A multidisciplinary team, consisting of a radiologist and a urologist experienced in tumor ablation, will perform each procedure. Depending on the size and location of the tumor, one to three antennas (Certus 140; NeuWave Medical, Madison, WI) will be used. The MW

system used for this study is the Certus 140 (NeuWave Medical, Inc., Madison, WI). The system is an FDA-approved, high-powered (140W in up to three channels) third-generation MW device that uses CO2 gas cooling to prevent shaft heating. The gas cooling also allows the probes to be stuck into tissue by creating a small ice ball at the tip using the Joule–Thomson method, similar to the tissue cooling mechanism of cryoablation systems. The probes are 17-gauge, and several different ablation zone configurations are available depending on which probe is selected. The expected ablation diameter in ex vivo tissue is available on the manufacturer's website (www.neuwave.com), but varies somewhat depending on the tissue type and tumor vascularity. If the tumor is in close proximity to adjacent structures, injectable grade dextrose 5% sterile water will be instilled through a spinal needle to increase the distance from the treatment zone (hydrodisplacement). For hydrodisplacement, the treatment team will consider the subjective proximity of structures as well as the expected ablation zone, which varies according to the manufacturer's specifications for the individual probe types. An ablation protocol utilizing the 65W power setting for 5 minutes will be used in the majority of patients. Ultrasound will be used for real-time monitoring of the extent of ablation to achieve a 5mm margin beyond the tumor, and immediate post-procedure imaging performed using contrast-enhanced CT (CECT) for all patients with adequate renal function. All patients will be admitted overnight for observation as per standard of care.

6.6 Tissue Sampling

Clinical pathologic evaluation
At the time of the initial diagnostic biopsy, a four quadrant biopsy will be performed per normal procedures. All tissue from the four quadrant biopsy will be processed per normal UW pathology procedures.

Research tissue sampling
If a clinical biopsy confirming renal cell cancer has not yet been performed, at the time of the clinical biopsy, 3 additional core biopsy samples will be obtained for research purposes. The samples will allow for creation of paraffin embedded, cryo-embedded and fresh frozen sections for evaluation of SBRT treatment response prior to microwave ablation.

During the microwave ablation procedure, 3 core biopsy samples will be obtained for research purposes. The primary tumor will be assessed for percent residual viable cells, the ratio of residual viable tumor to parenchyma, ratio of fibrotic stroma to tumor mass in the resected specimen, and immune cell infiltration, by the study team at a later date.

The research samples will be obtained and stored by the University of Wisconsin Carbone Cancer Center Translational Science BioCore (TSB-BioBank, University of Wisconsin Hospital Carbone Cancer Center, 1111 Highland Ave, Madison, WI 53705). The BioBank utilizes ONCORE for "registration" of the samples to the BioBank. Actual samples study samples(research core samples) will be coded with the study number, case # assigned by Radiation Oncolgy staff, and timepoint: 1 (pre-treatment) or 2 (post- XRT). All BioBank staff have undergone required human subjects training and HIPAA training. Actual specimens will be located within the BioBank in a room that is card access controlled with monitoring.

6.6.1. Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication

6.7 Duration of Therapy

Treatment with SBRT will be delivered over a period of two weeks, with radiation delivered two to three times per week. Four to six weeks after treatment, patients will be evaluated for microwave ablation by the treating radiologist with repeat CT or MRI imaging of the abdomen. Eight weeks after the conclusion of radiation treatment, patients will undergo microwave ablation, a single procedure. Adjuvant systemic treatment will be administered per institutional policies, physician recommendations, and patient preferences. Criteria for removal from study are described below.

6.8 Duration of Follow-Up: Refer to Table 2

After study enrollment, patients will undergo SBRT over a period of approximately 2 weeks. After 8 weeks, patients will undergo microwave ablation. Post treatment, patients will be followed as per standard of care. This will include a clinical visit four weeks after ablation, three months after ablation, six months after ablation, followed by visits every 6 months for a period of 3 years. Imaging will include either contrast-enhanced CT or MRI imaging at 3 and 6 months post therapy and every 6 months for 3 years. A BMP (including creatinine) will be obtained with imaging to evaluate renal function. Long term toxicity (specifically, nephrotoxicity, bowel obstruction, skin changes, and pain) will be assessed at these follow-up visits. Follow-up visits will be conducted by one of the treating physicians (radiation oncologist, interventional radiologist, or urologist) who will document physical exam, laboratory, and imaging findings as well as evaluate for toxicity. Any other evaluations prompted by symptoms, laboratory evaluation, or at the treating physicians' discretion may be performed as per standard of care. If a patient decides to withdraw from the study for non-treatment related reasons, no additional study-specific information will be obtained from the patient's future follow-up visit.

6.9 Criteria for Removal from Treatment

A patient's ongoing treatment on protocol will be temporarily or permanently withheld if any of the events below occur:

6.9.1. Illness that prevents further administration of treatment
6.9.2. Radiation dose constraints that are unable to be met at the current dose level.
6.9.3. DLTs or other unacceptable adverse events

6.9.4. Patient decision to withdraw from study
6.9.5. General or specific changes in patient's condition render the patient unacceptable for further treatment in the judgment of the treating physician or the study investigators

The reason for treatment stop/study removal and the date will be documented in a Case Report Form.

7. Measurement of Treatment

7.1 Toxicity Assessment

7.1.1. Dose-limiting toxicity (DLT) will be defined as grade 4 non-hematologic/grade 5 toxicity attributable to treatment , occurring until 30 days after ablation. Patients will be monitored and assessed for unexpected long-term toxicity during the post-treatment followup period. In the case of unexpected long-term toxicity, the dose level will be evaluated and potentially used to recalculate the MTD. Potential toxicities due to stereotactic body radiation therapy and microwave ablation are listed in Section 13.1 and 13.2 respectively. The most likely acute side effects of treatment include fatigue, nausea, vomiting, and pain due to the procedure. Toxicities not caused by treatment, such as pain due to tumor progression, will be excluded from the assessment.

7.2 Local Control

7.2.1. Imaging response will be measured as per the RECIST criteria[17]
- 7.2.1.1. Complete Response (CR) – Disappearance of entire target lesion
- 7.2.1.2. Partial Response (PR) – At least a 30% decrease in the sum of the diameters of the target lesion, taking as reference the baseline sum diameters.
- 7.2.1.3. Progressive Disease (PD) - At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression)
- 7.2.1.4. Stable Disease (SD) - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

7.3 Progression free survival defined with follow-up radiological assessment with progression free survival (PFS) calculated from the point of start of SBRT to the point of recurrence or death.

7.4 Overall survival (OS) defined from the point of start of SBRT to the time of death or last follow-up if alive.

7.5 Tumor pathology: H&E staining and pathologic evaluation for percentage of viable tumor remaining as measured by the presence of necrosis, fibrosis, hyalinization, and/or calcification, compared to pre-SBRT pathology.

8. Study Parameters

8.1 Patients will be followed for a minimum of three years with standard-of-care clinical visits, laboratory studies, and imaging. A study calendar is provided below. After treatment, patients will be seen for clinical follow-up at 1 month after treatment and then every 3 months until 6 months after treatment, at which point the visits will occur every 6 months until 3 years have passed, at which point further follow-up will be at the discretion of the treating physician.

Table 2: Study Calendar

	Pre-treatment (within 6 weeks of reg)	Wk 1	Wk 2	4-6 wk post SBRT	MWA [1]	1 month post MWA	Follow up visits[2]
Informed Consent	X						
Biopsy[4]	X						
MRI Clearance	X						
Radiation planning	X						
SBRT		X	X				
Microwave Ablation					X		
Demographics	X						
Medical History	X	X				X	X
Physical Examination	X		X	X		X	X
Vital Signs	X			X		X	X
Height	X						
Weight	X		X			X	X
ECOG Performance status	X	X	X	X		X	X
Complete blood count with differential count	X		X	X			
Basic Metabolic Panel	X			X		X	X
Adverse event evaluation		X	X	X		X	X
B-hCG for WOCBP	X						
Research Biopsy[3]	X				X		
Radiological evaluation/CT or MRI of Chest, Abdomen and Pelvis	X			X[5]			X[5]

[1]: MWA will be approximately 8 weeks post XRT

[2]: Followup: 3 months and 6 months post MWA then every 6 month for 3 years, then annually

[3]: Research biopsy sampling will be done at the time of the diagnositic biopsy (if not yet performed at time of consent) and at during the microwave ablation procedure

[4]: Clinical diagnostic biopsy does not have a "window". Patient must be treatment naïve for the renal cell carcinoma at time of study enrollment.

[5]: Imaging post ablation therapy will be at MD discretion, and in accordance with NCCN guidelines

9.0 Statistical Analysis

9.1 Number of patients

9.1.1 Phase IA – Nine (9) – eighteen (18) patients

9.1.1.1 We estimate that approximately 40-50 potentially eligible patients are seen at UWCCC each year. With a 3+3 study design and an estimated 20% rate of enrollment, we estimate it will take 1-2 years for patient accrual, treatment, and followup for determination of toxicity of the initial 9-18 patient Phase IA cohort.

9.1.2 Phase IB – Ten (10) patients

9.1.2.1 An additional ten patient, Phase IB expansion cohort will be accrued at the MTD at the conclusion of the Phase IA study to obtain further assessments of safety and provide preliminary estimates of local control rates to inform a potential Phase II study.

9.2 Study Endpoint(s)

9.2.1 Primary Endpoint of Phase I study:

9.2.1.1 Dose-limiting toxicity with SBRT combined with microwave ablation for renal cell carcinoma.

9.2.2 Secondary Endpoint(s) of Phase I study:

9.2.2.1 Local control rate

9.2.2.2 Progression free survival

9.2.2.3 Overall survival

9.2.2.4 Tumor pathology of post-SBRT specimen

9.3 Definition of end-points

9.3.1 Primary Endpoint of the Phase I study:

Dose-limiting toxicity (DLT) will be defined as grade 4 or higher non-hematologic toxicity attributable to treatment occurring until 30 days after ablation. This will exclude toxicities not caused by treatment, such as pain due to tumor progression. Toxicities will be defined per NCI CTCAE v5.0.

9.3.2 Secondary endpoints of the Phase I study:

9.3.2.1 Local control: Radiologic response per RECIST criteria and volumetric measurements.

9.3.2.2 Progression free survival defined with follow-up radiological assessment with progression free survival (PFS) calculated from the point of start of SBRT to the point of recurrence or death.

9.3.2.3 Overall survival (OS) defined from the point of start of SBRT to the time of death or last follow-up if alive.

9.3.2.4 Tumor pathology: H&E staining and pathologic evaluation for percentage of viable tumor remaining as measured by the presence of necrosis, fibrosis, hyalinization, and/or calcification, compared to pre-SBRT pathology.

9.4 Statistical Analysis

9.4.1 Primary objective of Phase I study:

A 3+3 design will be utilized for dose escalation. For each three patient cohort, DLT will be assessed as above. In the case of 0/3 DLTs, the dose will be escalated to the next level. In the case of 2/3 DLTs, the trial will be terminated with the previous level being the MTD. In the case of 1/3 DLTs, an additional three patients will be enrolled at the current dose level. If no additional DLTs are seen, the dose will be escalated to the next level. In the event of a total of 2 or more DLTs in 6 patients, the trial will be terminated with the previous dose level being the MTD. Toxicities will be tabulated by type and grade.

9.4.2 Secondary objectives of Phase I study:

9.4.2.1 Local control will be reported actuarially as a percentage with an associated 95% exact confidence interval.

9.4.2.2 Progression free and overall survival will be estimated using the Kaplan-Meier method. For calculation of PFS, patients without recurrence and alive at last follow-up will be censored at the date of the last radiologic assessment. For calculation of OS, patients alive at last follow-up will be censored. Log-rank test and Cox regression analysis will be used for univariate and multivariate analyses, respectively. Chi-square and regression analysis will be performed to test association of categorical variables with treatment response.

9.4.2.3 Tumor response will be reported via rates of complete response, partial response, and no response.

9.5 Justification for future studies

9.5.1 After study accrual, patient safety data will be analyzed to ensure treatment was well tolerated. If found to be acceptable, a larger Phase II study powered to detect a 15% increase in local control rates as compared to historical control, with a power of 80% and alpha of 0.1 would be initiated.

10.0 Pathology Review

Post-stereotactic body radiation therapy pathology will be obtained at the time of microwave ablation and compared to the samples obtained prior to treatment. This will be obtained in order to complete the correlative studies described above and to determine tumor response to radiotherapy treatment. These pre-ablation samples are collected for research puposes only and no tissue will be submitted to the UW Pathology department for clinical use.

Analysis of research samples

-Samples will be processed and scored per standard institutional practices University of Wisconsin Carbone Cancer Center Translational Science BioCore (TSB-BioBank). Paraffin embedded, cryo-embedded, and fresh frozen sections will be stored.

-Futrue analysis by the study team will include H&E staining and evaluation for percentage of viable tumor remaining as measured by the presence of necrosis, fibrosis, hyalinization, and/or calcification, and immune cell infiltration and compared to pre-SBRT pathology obtained at the time of original tumor diagnosis.

Tumor samples will be sent to the TSB-BioBank, University of Wisconsin Hospital Carbone Cancer Center, 1111 Highland Ave, Madison, WI 53705 per standard procedures

11.0 Data Collection/Storage/Confidentiality

Clinical trial coordinators in the Department of Human Oncology will do baseline data collection for each patient accrued into the protocol. The PIs, with the support of co-

investigators would collect specific disease, treatment and outcome related data, which will include:

Medical history including basic patient demographics as collected during registration, co-morbidities/habits and disease related variables including ECOG performance score, histological differentiation, tumor location, maximal tumor dimension as measured on diagnostic CT imaging, presence or absence of regional LN on diagnostic imaging, presence of metastatic disease at diagnosis, other pertinent findings on diagnostic imaging, stage, weight loss at presentation, baseline pain assessment, baseline laboratory parameters, treatment details, toxicity outcomes, treatment outcomes (clinical, radiological), and follow-up course.

The information collected for this study will be protected by limiting access to the data sheet to the study researchers. To ensure patient confidentiality information collected in this study will be kept on a secure computer within the Department of Radiation Oncology network, which is protected by a firewall that ensures the privacy of the network. Access to the information is limited to those listed in the protocol, all of whom have completed the requisite human subjects/HIPAA training and been given valid clinical access to this information.

Each subject will be assigned a research subject number, which is a code that can link the medical record number to the study data in the subject log. The subject log will be maintained on a secure password protected computer in the Department of Human Oncology. In addition to the principal investigators, the co-investigators will have access to the subject log.

12.0Patient Consent and Peer Judgment

Current FDA, NCI, state, federal, and institutional regulations regarding informed consent will be followed.

13.0 Safety Monitoring

13.1 Adverse Event List for SBRT

Likely

- Gastritis
- Nausea and vomiting
- Diarrhea
- Fatigue
- Loss of appetite and weight loss
- Mild radiation dermatitis

Less likely

- Pigmentation changes and fibrosis in the cutaneous, subcutaneous and deep visceral tissues in the radiation field
- Musculo-skeletal aches in the treatment fields.

Decrease in blood counts resulting in increased risk of infection, weakness, and/ or in bleeding and bruising easily
Hematuria

Rare but serious late effects
Bowel obstruction
Gastric, duodenal or small-bowel ulceration or perforation
Hepatotoxicity
Chronic Kidney Injury
Renal Hemorrhage
Transient myelopathy
Second malignancy

13.2 Adverse Event List for Microwave Ablation/Biopsy

Likely
Pain
Paresthesia
Post-ablation syndrome
Nausea
Vomiting
Malaise
Fever
Hematuria
Acute Kidney Injury

Less Likely
Hemorrhage
Hematoma

Rare but serious late effects
Bladder outlet obstruction
Bowel perforation or ulceration
Nephrotoxicity
Myelopathy
Chronic Kidney Injury
Ureteral damage
Tumor seeding

13.25 Adverse Event List for Biospy

Likely
Pain
Infection
A general feeling of discomfort
Blood in urine

Less Likely
Bleeding that requires a transfusion
Blood clot in the kidney

Rare but serious late effects
Difficulty passing urine due to damage to the kidneys and ureters
Permanent tingling/numbness in the area treated due to nerve damage

13.3 Adverse events characteristics

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE can be downloaded from the CTEP web site (http://ctep.cancer.gov).

'Expectedness': AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only.

Attribution of the AE:

Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

13.4 Adverse Event Reporting

Adverse events (AEs) and serious adverse events (SAEs) will be recorded in study database. All SAEs will be reported to the GU DOWG, UWCCC, and UW HS-IRB per policy. Reporting criteria are summarized in Table 3.

An AE is an undesirable medical occurrence (sign, symptom, or diagnosis) or worsening of a pre-existing medical condition (diabetes, congestive heart failure, rheumatoid arthritis) that occurs after initiation of the investigational product whether or not it is considered to be investigational product related. A worsening of an existing medical condition is one that was present at baseline (e.g., cancer, diabetes, migraine headaches, gout) and became more severe, more frequent, or increased in duration during investigational product treatment.

Expected events - Expected events are those that have been previously identified as resulting from treatment of renal cell cancer with radiation and MWA. These are defined above for acute and late toxicities (section 13.1). For purposes of this study, reporting requirements are determined by the assessment of the following adverse event characteristics: the type or nature of the event; the severity (grade); the relationship to the study therapy (unrelated, not likely, possibly, likely, or definitely related), and whether the event is expected or unexpected.

Recommended assessment steps include:
• Identification of adverse event.
• Determine whether the adverse event is expected or unexpected.
• Grading the severity of the adverse event using the appropriate set of criteria; CTCAE v5.0 (General, unexpected).
• Determination as to whether the adverse event is related to the study therapy using the following categories: Unrelated, Possible, Probable, and Definite

For the purpose of this study adverse event information will be collected through 30 day post MWA visit. After the 30 day visit only events specific late treatment effects will be collected.

We will continue to collect information on gastric, duodenal bowel and bladder ulcerations, perforations and obstructions, nephrotoxicity, myelopathy, ureteral damage tumor seeding and second malignancy's

An SAE is defined by regulatory agencies as one that suggests a significant hazard or side effect, regardless of the investigator or sponsor's opinion on the relationship to investigational product. This includes, but may not be limited to, any event that (at any dose):

1. Is fatal
2. Is life threatening (places the subject at immediate risk of death)
3. Requires inpatient hospitalization or prolongation of existing hospitalization
4. Is a persistent or significant disability/incapacity
5. Is a congenital anomaly/birth defect
6. Any event that does not exactly meet this definition yet, in the investigator's opinion represents a significant hazard can be assigned the "other significant hazard" regulatory reporting serious criteria
7. Additionally, important medical events that may not be immediately life threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the outcomes listed above, or result in urgent investigation, may be considered serious. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

Note: All deaths on treatment require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. "On treatment" is defined as during or within 30 days of completing protocol treatment (MWA).

All serious adverse events deemed to be related by the investigator to the SBRT or MWA (as listed in section 13.) will be collected and recorded throughout the study period beginning with the signing of the informed consent through the day patient is removed from the study or the date of death or three years after completion of the MWA (or the last SBRT treatment if surgery is not performed), whichever is earlier.

All serious adverse events that occur after the subject has signed the informed consent form must be reported to University of Wisconsin Carbone Cancer Center Data Safety and Monitoring Board and other regulatory agencies.

Serious adverse events occurring after conclusion of the study AND thought to be possibly related to the investigational study will be collected and reported within 10 working days of discovery or notification of the event via the same mechanism.

Table 3. Expedited reporting requirements for adverse events that occur within 30 days of the last protocol intervention.

FDA Reporting Requirements for Serious Adverse Events (21 CRF Part 312)

NOTE: Investigators **MUST** immediately report to the PI, *UWCCC and UW IRB per policy* ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). FDA Med Watch (3500A) will be submitted for grade 4 and 5 events at the discretion of the sponsor-investigator.

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

1) Death.
2) A life-threatening adverse event.
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria* **MUST** be immediately reported to the UWCCC within the timeframes detailed in the table below: With the exception of a 24 hr hospitalization for MWA procedure

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3 Time Frames	Grade 4 & 5 Timeframes
Resulting in hospitalization ≥ 24 hrs	Not required	10 Calendar Days	24 Hour; 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	10 Calendar Days	

- See section 13.0 for listing of toxicities
- Grade 3 toxicities during the 24hr hospitalization for MWA are exemption from SAE reporting

Expedited AE reporting timelines are defined as:

- **24-Hour; 5 Calendar Days** – The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.

- **10 Calendar Days** – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE

[1] Serious adverse events that occur more than 30 days after the last administration of investigational intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 10 working days for:

- All Grade 4, and 5 AEs

13.5 Stopping Rules

13.5.1 As described above, the study will use a standard 3+3 dose escalation design. For each three patient cohort, DLT will be assessed as above. In the case of 2/3 DLTs, the trial will be terminated with the previous level being the MTD. In the case of 1/3 DLTs, an additional three patients will be enrolled at the current dose level. In the event of a total

of 2 or more DLTs in 6 patients, the trial will be terminated with the previous dose level being the MTD.

13.6 Patient withdrawal

If a patient withdraws for any reason, a Case Report Form will be generated and filed.

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ELIGIBILITY CHECKLIST –

--------**(Y) 1.** Does the patient have a pathologically-confirmed diagnosis of renal cell carcinoma?

--------**(Y) 2.** Has the patient been deemed medically inoperable by his/her urologist?

--------**(Y) 3.** Is the tumor greater than 4 cm in greatest dimension per imaging?

--------**(Y) 4.** Is the patient over the age of 18?

--------**(Y) 5.** Has the patient provided written inform consent for study participation?

--------**(Y) 6.** Has the patient undergone complete pre-treatment work-up as listed in the protocol document (section 6.3)?

--------**(N) 7.** Does the patient have a history of any prior invasive cancer in the last 5 years (except for a diagnosis of low-risk prostate cancer post appropriate therapy, treated non- melanoma/melanoma skin cancer, appropriately treated ductal carcinoma in situ or early stage invasive carcinoma of breast and appropriately treated in-situ or early stage cervical/endometrial cancer), OR any prior radiation therapy to the upper abdomen?

--------**(N) 8.** Is the patient a pregnant or nursing woman?

--------**(Y) 9.** If the patient is a woman of childbearing potential, are they agreeable to the use of contraceptive methods (hormonal or barrier method of birth control; abstinence) from the point of study entry and for the duration of completion of all active treatments? Should a woman become pregnant or suspect she is pregnant while participating in this study, is she willing to inform her treating physician immediately?

--------**(N) 10.** Has the patient received any treatment with a non-approved or investigational drug within 28 days of study treatment?

--------**(N) 11.** Is the patient's ECOG performance score < 2?

--------**(Y) 12.** Has the patient passed the MRI screening process?

The following questions will be asked at Study Registration:

--------(Y). Has the Eligibility Checklist *(above)* been completed? Is the patient eligible for this study?

----------Date the study-specific Consent signed

----------Patient's Name

----------Patient's UWHC MRN

---------- Patient's Date of Birth

---------- Patient's zip code

The Eligibility Checklist will be completed in its entirety prior to enrollment on study. The completed, signed, and dated Checklist used at study entry must be retained in the patient's study file.

_____ _____

Completed by Date

_____ _____

Verified by Date

Oversight And Monitoring Plan

The UWCCC Data and Safety Monitoring Committee (DSMC) is responsible for the regular review and monitoring of all ongoing clinical research in the UWCCC. A summary of DSMC activities are as follows:

- Reviews all clinical trials conducted at the UWCCC for subject safety, protocol compliance, and data integrity.
- Reviews all Serious Adverse Events (SAE) requiring expedited reporting, as defined in the protocol, for all clinical trials conducted at the UWCCC, and studies conducted at external sites for which UWCCC acts as an oversight body.
- Reviews all reports generated through the UWCCC DSMS elements (Internal Audits, Quality Assurance Reviews, Response Reviews, Compliance Reviews, and Protocol Summary Reports) described in Section II of this document.
- Notifies the protocol Principal Investigator of DSMC decisions and, if applicable, any requirements for corrective action related to data or safety issues.
- Notifies the CRC of DSMC decisions and any correspondence from the DSMC to the protocol Principal Investigator.
- Works in conjunction with the UW Health Sciences IRB in the review of relevant safety information as well as protocol deviations, non-compliance, and unanticipated problems reported by the UWCCC research staff.
- Ensures that notification is of SAEs requiring expedited reporting is provided to external sites participating in multi-institutional clinical trials coordinated by the UWCCC.

Monitoring And Reporting Guidelines

UWCCC quality assurance and monitoring activities are determined by study sponsorship and risk level of the protocol as determined by the PRMC. All protocols (including Intervention Trials, Non-Intervention Trials, Behavioral and Nutritional Studies, and trials conducted under a Training Grant) are evaluated by the PRMC at the time of committee review. UWCC monitoring requirements for trials without an acceptable external DSMB are as follows:

Intermediate Monitoring

Protocols subject to intermediate monitoring generally include UW Institutional Phase I/II and Phase II Trials. These protocols undergo review of subject safety at regularly scheduled DOWG meetings where the results of each subject's treatment are discussed and the discussion is documented in the DOWG meeting minutes. The discussion includes the number of subjects enrolled, significant toxicities, dose adjustments, and responses observed. Protocol Summary Reports are submitted on a semi-annual basis by the study team for review by the DSMC.

Review and Oversight Requirements

Serious Adverse Events requiring reporting within 24 hours (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu within one business day. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if immediate action is required. Within 10 working days, all available

subsequent SAE documentation must be submitted electronically along with a 24 hour follow-up SAE Details Report and a completed UWCCC SAE Routing Form to saenotify@uwcarbone.wisc.edu. All information is entered and tracked in the UWCCC database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC.

If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor-investigator, the PI reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators.

For a multiple-institutional clinical trial the PI is responsible for ensuring SAEs are reported to the FDA as well as to all participating investigators

Serious Adverse Event-Reported within 10 Days
Serious Adverse Events requiring reporting within 10 days (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if further action is required. All information is entered and tracked in the UWCCC database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC.

If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor-investigator, the PI reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators.

For a multiple-institutional clinical trial the PI is responsible for ensuring SAEs are reported to the FDA as well as to all participating investigators.

Sponsor-Investigator Responsibilities for SAE Review
In the event the UWCCC Principal Investigator is acting as the Sponsor-Investigator (i.e., the PI holds the IND), the PI assumes responsibilities of the study sponsor in accordance with FDA 21 CFR 312.32. In this capacity, the UWCCC PI reviews all reports of serious adverse events occurring on the study at the UWCCC and participating external sites and makes a determination of 1) **suspectedness** (i.e., whether there is a reasonable possibility
That the drug caused the AE); and 2) unexpectedness in the context of theis study. SAE with suspected causality to study intervention deemed unexpected are reported as IND safety Reports by the UWCCC PI to the FDA, all participating investigators on the study, within 15 calendar days. All fatal or life-threatening SAE that are unexpected and have suspected causality to the study intervention will be reported by the UWCCC PI to the FDA, all participating investigators on the study within 7 calendar days.

Study Progress Review
Protocol Summary Reports (PSR) are required to be submitted to the DSMC in the timeframe determined by the risk level of the study (quarterly; semi-annually; or annually). The PSR provides a cumulative report of SAEs, as well as instances of non-compliance, protocol deviations, and unanticipated problems, toxicities and responses that have occurred on the protocol in the timeframe specified. PSRs for those protocols scheduled for review are reviewed at each DSMC meeting.

Protocol Summary Reports enable DSMC committee members to assess whether significant benefits or risks are occurring that would warrant study suspension or closure. This information is evaluated by the DSMC in conjunction with other reports of quality assurance activities (e.g., reports from Internal Audits, Quality Assurance Reviews, etc.) occurring since the prior review of the protocol by the DSMC. Additionally, the DSMC requires the study team to submit external DSMB or DSMC reports, external monitoring findings for industry-sponsored studies, and any other pertinent study-related information.

In the event that there is significant risk warranting study suspension or closure, the DSMC will notify the PI of the DSMC findings and ensure the appropriate action is taken for the protocol (e.g., suspension or closure). The DSMC ensures that the PI reports any temporary or permanent suspension of a clinical trial to the sponsor (e.g., NCI Program Director, Industry Sponsor Medical Monitor, Cooperative Group Study Chair, etc.) and other appropriate agencies. DSMC findings and requirements for follow-up action are submitted to the CRC

EXPEDITED REPORTING OF SERIOUS ADVERSE EVENTS
Depending on the nature, severity, and attribution of the serious adverse event an SAE report will be phoned in, submitted in writing, or both according to Table below. All serious adverse events must also be reported to the UWCCC Data and Safety Monitoring Committee Chair. All serious adverse events must also be reported to the UW IRB (if applicable), and any sponsor/funding agency not already included in the list.

Determine the reporting time line for the SAE in question by using the following table. Then refer to sections A and B below if the SAE occurred at the UWCCC or sections C and D if the SAE occurred at 1 South Park, Johnson Creek, or a WON Site.

SAE Requiring *[24]* Hour Reporting Occurs at UWCCC:

1. Report to the UWCCC:
Reference the **SAE SOP** (Standard Operating Procedure) and the **SAE Reporting Workflow for DOWGs** on the UWCCC website (http://www.uwccc.wisc.edu) for specific instructions on how and what to report to the UWCCC for *[24]* hour initial and follow-up reports. **A follow-up report is required to be submitted within 5 days of the initial *[24]* hour report.**
For this protocol, the following UWCCC entities are required to be notified:
a) saenotify@uwcarbone.wisc.edu
b) *Dr. Mike Bassetti, UWCCC PI*
c) *Diana Trask, UWCCC Radiotherapy PM*
d) Any other appropriate parties listed on the SAE Routing Form (for follow-up reports only)

2. **Report to the IRB:**
Consult the UW-IRB website for reporting guidelines

SAE Requiring *[10]* Day Reporting Occurs at UWCCC:
1. Report to the UWCCC:
Reference the **SAE SOP** and the **SAE Reporting Workflow for DOWGs** on the UWCCC website (http://www.uwccc.wisc.edu) for specific instructions on how and what to report to the UWCCC for *[10]* day reports.

For this protocol, the following entities are required to be notified:

a) saenotify@uwcarbone.wisc.edu
b) Any appropriate parties listed on SAE Routing Form

2. Report to the IRB:

Consult the UW-IRB website for reporting guidelines.

Other Reporting Requirements

Reporting to the FDA

Serious Adverse Events occurring on studies on which a UW PI is acting as sponsor-investigator must be reported to the FDA within the appropriate time frame. Mandatory and voluntary reporting guidelines and instructions are outlined on the FDA website:
http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

Expedited reporting requirements for adverse events that occur within 30 days of the last dose of radiation therapy[1]

FDA Reporting Requirements for Serious Adverse Events (21 CRF Part 312)

NOTE: Investigators **MUST** immediately report to the PI, *UWCCC and UW IRB per policy* ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). FDA Med Watch (3500A) will be submitted for grade 4 and 5 events at the discretion of the sponsor-investigator.

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

7) Death.
8) A life-threatening adverse event.
9) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
10) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
11) A congenital anomaly/birth defect.
12) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria* **MUST** be immediately reported to the UWCCC within the timeframes detailed in the table below: With the exception of a 24 hr hospitalization for MWA procedure

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3 Time Frames	Grade 4 & 5 Timeframes
Resulting in hospitalization ≥ 24 hrs	Not required	10 Calendar Days	24 Hour; 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	10 Calendar Days	

- See section 13.0 for listing of toxicities
- Grade 3 toxicities during the 24hr hospitalization for MWA are exemption from SAE reporting

Expedited AE reporting timelines are defined as:

- **24-Hour; 5 Calendar Days** – The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- **10 Calendar Days** – A complete expedited report on the AE must be submitted within 5 calendar days of learning of the AE

[1] Serious adverse events that occur more than 30 days after the last administration of investigational intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 10 working days for:

- All Grade 4, and 5 AEs