CASE COMPREHENSIVE CANCER CENTER

Study Number:	CASE 12806
Clinicaltrials,gov #:	NCT00458484
Title:	Evaluation of a Radiosurgical Approach for the Treatment of Kidney Tumors in Poor Surgical Candidates
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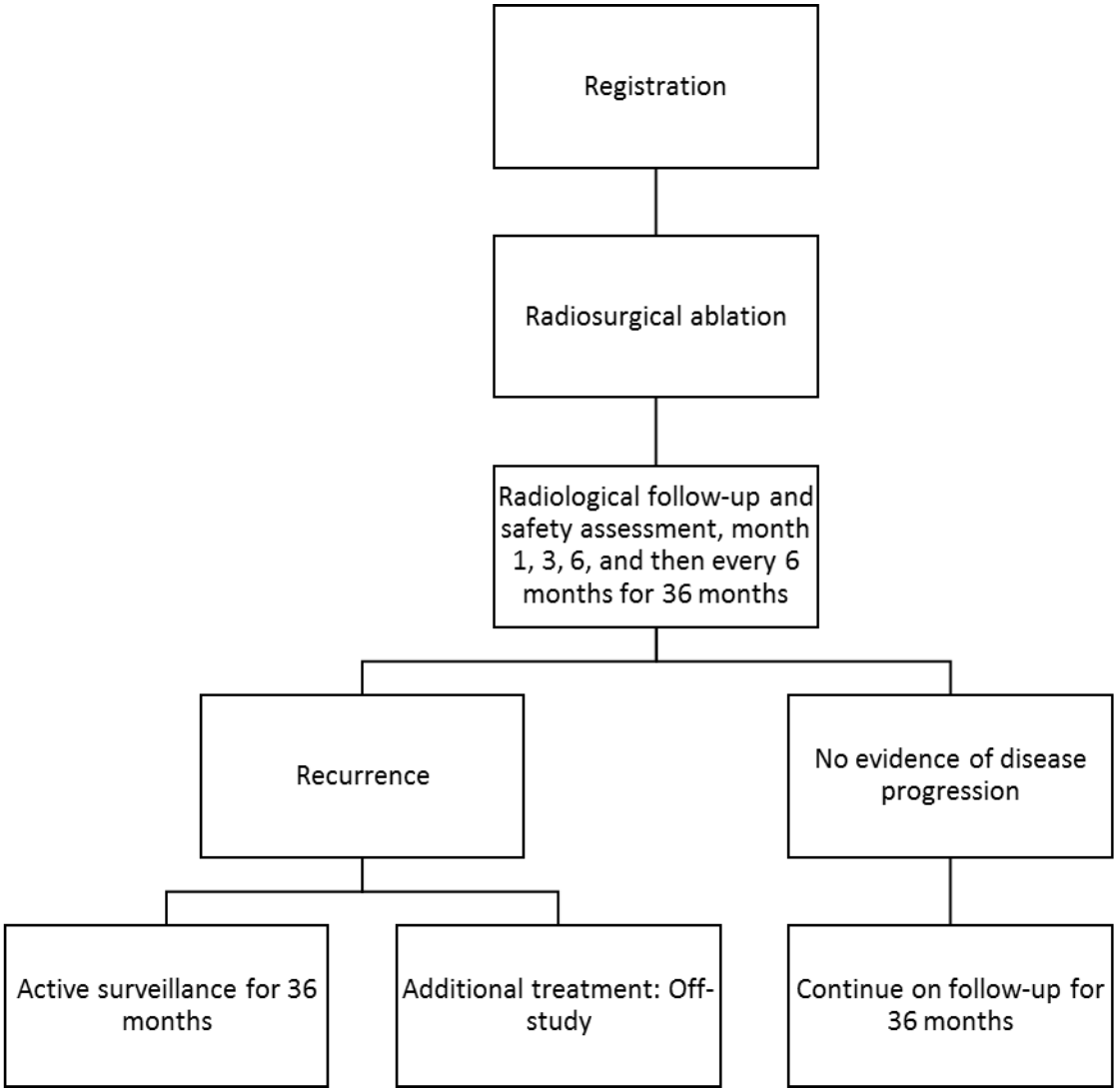
Sponsor:	Case Comprehensive Cancer Center

Summary of Changes

Protocol Date	Change
1.9.2007	• Initial IRB approval
11.20.2009	• Fred Barton added as co-investigator
3.25.2010	• Changed Frequency of Radiation (now 4 days instead of 2) • update to CTCAE version 4.0 • Administrative changes made for clarification throughout
7.30.2010	• Rodney Ellis added as co-investigator
12.10.2010	• EMR access updated
5.25.2011	• Simon Lo added as co-investigator • dose descriptions standardized throughout protocol • clarifications to eligibility • pretreatment timeframe clarified • added second series of patients • Dose escalations added
11.15.2012	• changed PI to Rodney Ellis • revised inclusion criteria • revised study calendar • clarified AE reporting
4.12.2013	• Addition of blood correlative • Clarified previous radiation treatment location for eligibility, • Clarified the need for additional radiologic work up to determine renal function prior to treatment • Clarified post-treatment cryoblation option
7.25.2013	• Schema revised • post treatment section clarified • patient calendar updated • tumor measurement process clarified
8.31.2014	• Included fiducial marker information and removed ultrasound option in pre-treatment. • Included chest in the MRI in calendar to match protocol. • Added Appendix 1
1.24.2017	• Updated template • Removed outdated references to Case and Cancer IRB • Updated staff who can do tumor measurements • Included Linac based SBRT as radiotherapy option

Table of Consents

SCHEMA


Registration
Radiosurgical ablation
Radiological follow-up and safety assessment, month 1, 3, 6, and then every 6 months for 36 months
Recurrence
No evidence of disease progression
Active surveillance for 36 months
Additional treatment: Off-study
Continue on follow-up for 36 months

1.0 INTRODUCTION

Each year in the United States, approximately 31,000 cases of kidney on upper urinary tract cancer occur, resulting in more than 11,900 deaths[1]. These tumors account for approximately 3 percent of adult malignancies and occur in a male-female ratio of 1.5 is to 1. Although most cases occur in persons aged 50 to 70 years, renal carcinoma has been observed in children as younger 6 months. Between 1975 and 1995, a steady and significant increase in the incidence of renal carcinoma was seen, from 2 percent to 4 percent per year, and increase of 42 percent since 1973.

Surgery is the only known effective therapy for localized renal carcinoma. The standard procedure today for treatment of localized renal carcinoma is radical nephrectomy. Radical nephrectomy involves complete removal of Gerota's fascia and its contents, including the kidney and the adrenal gland, and provides a better surgical margin than simple removal of the kidney.

Laparoscopic nephrectomy is a less invasive procedure for the removal of kidneys with a small volume of RCC[2,3,4].

Radio surgical ablation of renal tumors offers a noninvasive alternative for treatment of renal malignancies. Radiosurgery is precisely delivered pinpoint radiation using an external stereotactic guidance and hypo-fractionated high-dose radiation in an attempt to ablate the kidney cancer.

In an initial preclinical evaluation, radiosurgery for extracorporeal renal tissue ablation was very promising and demonstrated its ability to ablate a targeted area precisely and completely with relative sparing of the surrounding tissue[5].

Clinical experience with radiosurgery for renal tumors is limited. In a recent report[6] 20 patients, age ranged from 31 to 85 years (mean 62), had 27 cancers treated with a volume ranging from 2.4 to 1366cc (mean 367cc). Patients were most commonly treated with 8 Gy times 5 fractions. The control rate was 93% with follow-up ranging from 2 to 45 months (mean 12 months). The survival or regrowth of tumor vasculature has been suggested to be a major determinant of radiation responses (Huang 2010 and Du 2012).

To evaluate each patient's prognostic potential we will measure MIF (both MIF-1 and MIF-2) and VEGF levels before and after radiation therapy to determine if these serum markers may give a predictive indication of tumor response.

2.0 OBJECTIVES

Primary objective: To evaluate and compare the clinical safety of utilizing four different schemes of radiosurgical ablative techniques for treating poor surgical candidates with renal tumors.

Secondary Objective: To evaluate and compare the clinical and radiographic efficacy of four different schemes of radiosurgical ablation of renal tumors in poor surgical candidates.

Serum Blood Marker Objective: To determine if serum markers collected before and after radiation may give a predictive indication of tumor response.

3.0 PATIENT SELECTION

Conditions for Patient Eligibility

- Patient is considered a poor surgical candidate for removal of renal mass as determined by anesthesiology pre-operative assessment or the surgical team, or medical team. (No major psychiatric illnesses.)
- Patient is $\geq$ 18 years of age.
- Patient is able to give and sign study specific informed consent.
- No prior radiation to the treatment field.
- Negative serum or urine pregnancy test within 72 hours prior to registration for women of childbearing potential.
- Patient has a radiologically and /or pathologically confirmed diagnosis of a renal tumor
- Karnofsky status of $\geq$ 60%
- Signed study-specific informed consent prior to study entry.

All/any clinical, radiological and pathological data for the patient will be reviewed and the study investigators will assess suitability for treatment with radio-surgical technique. If the eligibility criteria are met, the patient will be scheduled for a treatment planning session.

Conditions for Patient Ineligibility

- Any patient not meeting the eligibility criteria.
- Any patient with active connective tissue disease such as lupus, dermatomyositis.
- Any patient with active Crohn's disease or active ulcerative colitis.
- Major psychiatric illness, which would prevent completion of treatment or interfere with follow-up.

4.0 PRE-TREATMENT EVALUATIONS

- History and physical and KPS (Appendix 1).
- Patients have confirmed renal mass on imaging. The patients will be registered through the Seidman Cancer Center Clinical Trials Unit (CTU) in Oncore. Preoperative testing will be done to assess the patient's eligibility for radio-surgical treatment, locate the tumor, and evaluate its accessibility by this approach prior to the radiation treatment planning date.
- Imaging of the kidney will be obtained to evaluate the kidney prior to planning by CT or MRI of the chest and abdomen with or without contrast. Fiducial markers will be placed

prior to treatment, with consideration for repeat or initial biopsy. CT scan of chest and abdomen should be obtained for staging prior to treatment.

- Multiple percutaneous needle biopsies of the renal tumor will be obtained under radiological guidance. After the biopsies are obtained, 2-3 fiducials may be placed in or near the tumor via the 18 gauge needle, for image guidance purposes, alternatively, fiducial placement may be performed as a separate procedure in patients having pathology confirmed disease at the time of presentation for radiation therapy planning.
- It is preferable that the patient have their pathology review done at University Hospitals Cleveland Medical Center.
- All clinical, radiological and pathological data for the patient will be reviewed and suitability for treatment with radio surgical technique will be assessed. If the eligibility criteria are met, the patient will be registered in the study after obtaining informed consent.
- Radiological work up will be performed to evaluate for metastatic disease if clinically indicated.
- Radiological work up will be performed to evaluate baseline renal function prior to the start of radiation therapy if clinically indicated.

5.0 REGISTRATION PROCEDURES

Approximately 32 subjects will be enrolled onto this study; four to eight individuals will be assigned to one of four different categories for comparisons to be made; an additional series of 12 patients will be enrolled in groups of 4 and assigned to three different categories. Patients can be registered only after the eligibility criteria are met. In addition, the following information must be provided:

- Patient's name and ID number.
- Verifying Physician's Name.
- Demographic Data.
- Treatment planning and start date.
- Eligibility criteria information.
- Patient's consent to enroll in the study
- All eligibility source documentation and checklist will be sent to the CTU QA office for review prior to subject enrollment

6.0 RADIATION THERAPY

Patient will have a treatment planning session for delivery of radiosurgical treatments and an immobilization device will be custom made for every patient, per standard of care. Specification of patient immobilization for each radiation treatment will conform to institutional practice.

Serum Blood Markers:
Patients will be asked to participate in ELISA blood testing just prior to and immediately following each daily radiation therapy session. Approximately 5cc of blood will be collected

within 2 hours prior to and following completion of fractionated radiation therapy to assess the levels of MIF (both MIF-1 and MIF-2) and VEGF. This whole blood will be separated into plasma and rapidly frozen at -80 C using standard procedures. At later time points, plasma samples will be thawed and subjected to an ELISA for each of the markers using commercial kits and standards. Given that survival or regrowth of tumor vasculature has been suggested to be a major determinant of radiation responses, measurement of VEGF levels prior and following radiation, these tests may give a predictive indication of tumor response.

Pending patient approval, we will also store remaining plasma samples for detection of additional cancer markers to potentially improve our ability to predict for response to therapy with new tumor markers.

Radiation Doses:
Radiation will be delivered in 4 fractions. The initial dose level will be 6 Gy per fraction to a total dose of 24 Gy in 4 fractions. Doses will be escalated at 2 Gy per fraction increments to 12 Gy per fraction to a total dose of 48 Gy. The radiation treatment planning and evaluation details are appended.

Series I:
Twenty patients who are not surgical candidates will be offered treatment with a radio-surgical technique. Four patients will be registered in each dose group. Treatments will be initiated with 4 patients utilizing the minimum dose and observe what happens. If no DLTs are observed, then escalation to the next set of 4 patients to the next initial dose level will occur. If 1 DLT is observed, treatment of the next set of 4 patients at the same dose level will occur. If zero or 1 additional DLTs are observed, then dose escalation occurs as previously described. However, if $\geq$ 2/4 or $\geq$ 3/8 are observed at a given dose level the trial stops. On average, this results in between 4-5 patients being treated before escalation. The table below shows the probability of stopping giving an underlying toxicity level using this design.

Table: Probability of stopping escalation given underlying toxicity

Underlying Pr(Toxicity)	**0.1**	**0.2**	**0.25**	**0.3**	**0.35**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**
Pr(Stopping)	0.07	0.25	0.37	0.49	0.61	0.71	0.86	0.95	0.99	0.998	0.999

If a patient fails original treatment, he or she will be either kept on study for observation, or if they require retreatment, they will be taken off study.

Series II
The next series will be reached if insufficient dose limiting toxicities have occurred upon completion of the initial dose escalation series I to a total dose of 48 Gy in 4 fractions to warrant limitation of further dose escalation.

At this level, if normal tissue toxicities for SBRT have not proven to be problematic for renal lesions, then “standard” dose and fractionations will be prescribed for subsequent patients as would be used for example in Lung cancer. Given the 90% expectant local control for lung

lesions given 20 Gy in 3 fractions, we are highly anticipating reaching an efficacious dose during series II of the trial. If the 12 Gy x 4 fraction cohort is irradiated without dose limiting toxicities, then 12 additional patients will be accrued for further dose escalation following dose toxicity criteria defined below:
Based on the Linear Quadratic Model commonly used for radiobiologic comparisons, each subsequent group of four participants will receive further dose escalation using a 3 fraction regimen to increase beyond 48 Gy in 4 fractions in 20% dose equivalent increments.

The first group of four patients at this level (Series II) will receive 48 Gy to the target volume (tumor) in 3 fractions of 16 Gy per fraction. If acute toxicity is acceptable, then the next four patients will be escalated to 54 Gy in 3 fractions of 18 Gy. Finally if a dose limit has not been reached, the last group of four patients will be treated to 60 Gy in 3 fractions of 20 Gy each.

It is important to note that dose to the normal tissues surrounding the target has not been allowed to dose escalate. Tolerance levels selected for these normal organs (see Table I. and Appendix I., are consistent with RTOG standards and normal tissue limits approved for UHCMC Protocol Case 13807 associated with Prostate Cancer with Cyberknife or Linac based SBRT irradiation.

Table I. Dose Specifications for Normal Organs (and Appendix I.)

1. Bowel – No more than 1 cc can receive 8 Gy/fx for a total of 24 Gy in 3 to 4 fractions.
2. Cord – No more than 0.3 cc can receive 6.7 Gy/fx for a total of 20 Gy in 3 to 4 fractions.
3. Stomach - No more than 1.0 cc can receive 7.3 Gy/fx for a total of 22 Gy in 3 to 4 fractions.
4. Liver – No more than 2/3 of liver volume can receive 5.7 Gy/fx for a total of 17 Gy in 3 to 4 fractions. Additionally within that volume – 800 cc should not receive more than 5.0 Gy/fx for a total of 15 Gy in 3 to 4 fractions.
5. Contralateral Kidney- No more than 5 % of the volume can receive more than 4.7 Gy/fx for a total of 14 Gy in 3 to 4 fractions.

It is thought that superior Cyberknife or Linac based SBRT treatment plans and delivery for this current cohort may be achievable without any increase in normal tissue toxicity as defined above. If this is not the case for any of the 12 patients included in the new series of cohorts and where the treatment plan has been determined to fail, the patient target volume dose will be reduced to the previous cohort dose. In no case will a dose escalation occur if the normal tissue toxicities criteria are not met in the treatment plan.

If 3 successive patients fail to meet the treatment planning criteria, the dose escalation study effort will be terminated and successive remaining patients will be treated at target dose from the previous cohort of 4 patients.

For this second series of the study, patients who fail by evidence of tumor regrowth or metastatic dissemination will not be retreated to the current dose level. However, if the subject experiences

recurrence or progression, they will either be followed by observance; or if they require retreatment, they will be taken off study.

Radiation Toxicity:
All patients should be seen at 1, 3 and 6 months ± 2 weeks, and then every 6 months by either the radiation oncologist or the urologist to evaluate radiation toxicities, or arranged to be seen locally if unable to return to Cleveland Medical Center with reports sent back for review. At 6 months post SBRT, the patient will be scheduled to be seen in Urology to evaluate their response to the therapy with imaging and an optional biopsy. Urinary and bowel irritation manifested as urgency, frequency, dysuria, infection and incontinence will be recorded. Medications to treat radiation side-effects will be recorded as well as dose and frequency. Acute Radiation Toxicity (<180 days from treatment date) will be documented using NCI common toxicity criteria, version 4.0. A shorter period of toxicity assessment for the purposes of dose escalation will be used. This will be done at the 1, 3 and 6 month follow-up visits after radiation therapy. More delayed short-term toxicities would be used in the final determination of the recommended Phase II dose.

Dose limiting Toxicity:
Acute Radiation Toxicity ≥ grade 3 in the Gastrointestinal and renal/genitourinary categories of the common terminology criteria for adverse events 4.0 (CTCAE) will be considered dose limiting (see above). The maximum tolerated dose will be one dose level below which the adverse event, as described above, occurred (See statistical section).

7.0 PATIENT ASSESSMENTS

Follow-up schedule and parameters assessed will be as follows:

		Treatment			Months Post-RT							
Parameters	**Screening**	**Dose 1**	**Dose 2**	**Dose 3**	**1**	**3**	**6**	**12**	**18**	**24**	**30**	**36**
History & Physical	X				X	X	X	X	X	X	X	X
Pregnancy Test	X											
Toxicity Evaluation					X	X	X	X	X	X	X	X
Biopsy	X						X[2]					
MRI or CT of chest and Abdomen	X						X	X	X	X	X	X
Radiotherapy		X	X	X								
ELISA Blood Draws [1]		X[1]	X[1]	X[1]								

[1] To be drawn within 2 hours prior to and following completion of fractionated radiation therapy

[2] Patient will be given the option to have this procedure between 6 to 12 months follow up post RT. Standard stains with H & E as well as any staining to access tissue viability will be ordered as available to possibly include NADH

(marker of metabolism) and MIB-1 (proliferation marker) or propidium iodide, which is a marker of cell membrane integrity and thus, death.

Post-Treatment Follow-up Schedule

After radio-surgery, follow-up will be done at 1, 3 and 6 months and then every 6 months post radiosurgery for a total of 36 months.

If viable tumor is identified or enhancement on any post therapy follow-up CT or MRI is identified, the patient may be offered additional treatment or observation, based on imaging analysis or patient preference and co-morbid illness clinical status. If the patient receives any re-treatment, they will be taken off study.

Radiation treatments for this subject will cease if any DLT's occur. The patient will then be followed every 6 months until 36 months after the radiation treatment.

Between 6 to 12 months following the end of RT, an optional percutaneous renal biopsy of the target tumor under US or CT guidance will be offered.

Acute vs. Late Toxicity

Acute toxicity monitoring: Acute side effects ($\leq$ 180 days from RT start) will be documented using the using the NCI Common Toxicity Criteria version 4.0. (CTCAE)

Late toxicity monitoring: All late (> 180 days from RT start) side effects will be evaluated and graded according to the. NCI Common Toxicity Criteria version 4.0. (CTCAE)

8.0 DATA COLLECTION

All study-related data will be entered into OnCore. Access will be limited via a password known only to the investigator and designated research personnel (study nurse(s), data manager(s)).

9.0 STATISTICS

Statistical Considerations

The primary goal of this study is to compare and evaluate toxicities across four varied treatment schemes using a dose escalation design with four cohorts of 4-8 patients each. Escalation to the next dose will take place if no DLT's are observed in the first four patients treated at the current dose. If 2 or more DLT's are observed in the first four patients, then escalation is stopped. If 1 DLT is observed , then four more patients are treated at the same dose, and dose escalation stops if 2 or more of these next four (3/8 of patients treated at that dose) experience a DLT. If the probability of a DLT is 40%, there is a 71% chance of stopping at the current dose, whereas if the probability of DLT is 10%, there is only a 7% chance of stopping the dose escalation.

All analyses of the data will be descriptive. Clinical and radiographic efficacy will be summarized by calculating Kaplan-Meier curves for the following: overall survival, disease-free

survival, time to local progression, time to distant failure. Data from all dose groups will be pooled in these analyses. Survival rates estimated from the Kaplan-Meier curves will be estimated with 95% confidence intervals. Rates of acute and late side effects and adverse events will be summarized as proportions, with 95% confidence intervals.

Sample Size
The number of patients studied in this trial is determined by the dose escalation strategy and the number of DLT's that are observed at each dose level. With four dose levels and cohorts of 4-8 subjects per dose, the minimum sample size is 2 and the maximum is 32. It is expected that around 20 subjects will be enrolled. This design with cohort sizes of 4-8 per dose ensures that the probability of escalating to the next dose is .93 when the probability of DLT is .1, but is only .05 when the probability of a DLT is .6.

10.0 COSTS AND COMPENSATION

The costs of procedures, tests, visits and hospitalizations in connection with the radiosurgery treatments are standard of care and will be billed to the subject's insurer and/or to the subject (regardless of which group the subject is placed into). Costs for pre-treatment diagnostic scans, radiation therapy treatments, and post-operative follow-up are also standard of care and will be charged accordingly. Therefore, subjects and their insurers will be fully responsible for the costs related to this research evaluating and comparing standard of care procedures. Subjects will not be paid for their participation in this study.

11.0 RISKS

Risks include those that result from the special nature of radiosurgery standard of care, including errors in giving the radiation. This may include giving radiation to normal tissue around the tumor and not to the cancer, or giving the wrong dose of radiation, either too much or too little. Any of these problems could potentially be severe, possibly even fatal. There may be risks from assigning a subject to one of the four research categories versus any one of the other three options. The research physician cannot pre-determine which category is best for any individual patient as a purpose of this study is to evaluate and compare the four options.

The use of radiation in any form is also associated with a small risk of causing another cancer, either in the portion of the body directly exposed to radiation during treatment (the target of treatment), or in other sites of the body due to low doses of scattered radiation. Depending on which category a subject is assigned, the risk may be greater or smaller for one subject than for others in the study.

Because radiosurgery for treating a kidney tumor is a very new approach, there may be other risks that we are not yet aware of, some of which could potentially be severe.

All data entered into the computer will be coded and personal identifiers will be removed. All data that can be linked to an individual will be protected and the master list will be stored off-line

and will be available only to the principal investigator or his or her designee(s). Although every effort will be made to protect and maintain confidentiality, there is a slight risk of loss of confidentiality.

12.0 DATA SAFETY AND MONITORING

Clinical information from subjects will be recorded onto Case Report Forms and subsequently transferred into OnCore. Patients who additionally consent to a separate Urology Registry will have their data added to the Urologic Oncology & Minimally Invasive Therapies Database for UHHS Faculty (UHCMC IRB No. DBR0006-CC031).

Should any unanticipated adverse device events occur during the course of the study, the clinical research coordinator will ensure that they are documented by the investigator and reported to the University Hospitals Cleveland Medical Center Institutional Review Board (UHCMC IRB) per its then-current guidelines. An unanticipated adverse event is defined by the FDA as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol (including a supplementary plan), or any other unanticipated serious problem with a device that relates to the rights, safety, or welfare of subjects. If the determination is made that an unanticipated adverse event presents an unreasonable risk to subjects, the clinical evaluation will be paused, or if deemed appropriate (to enable further investigation), the subject will be withdrawn as soon as safely possible.

Adverse events, grade 2 and above, will be captured in OnCore and will be reported in accordance with the Data and Safety Monitoring Plan (DSMP) that is approved by the Cancer Center Protocol Review and Monitoring Committee (and aligned with the NCI-approved plan). All monitoring and reporting will be compliant with policies presented in the most current version of the CCCC Clinical Trials Operations Manual, so that an independent assessment can be made of study activities. The study will be updated to remain compliant with any changing rules/policies of the CCCC.

All serious adverse events (SAE's), and IRB continuing renewals including review of toxicity will be promptly submitted to the University Hospitals Cleveland Medical Center IRB.

Tumor measurements will be defined by the principal investigator or treating physician and confirmed by a radiation oncologist or radiologist not associated with this study. In addition, responses will be reported directly to the CCCC Data Safety and Toxicity Committee (DSTC) for confirmation of objective responses reported. Submissions will be made within accordance with reporting timelines. The study PI, co-investigators, and/or research staff will monitor all patients on the trial, and will evaluate patients at each treatment encounter and in follow-up. Serious adverse events are reported to the attending physician, the Principal investigator (PI), the DSTC, and the UHCMC IRB per IRB guidelines.

Accessing Electronic Medical Records
This study will access both paper and electronic medical records systems to obtain medical information for the subjects. Therefore, electronic medical records must be utilized to obtain medical information in a timely manner. The names will come from surgeon's offices (staff and records), tumor boards, surgical schedules, IDX and the surgeon's direct referral. Each patient will be approved by the surgeon before contact by the research individual occurs. Physician Portal, EMR and paper charts will be used to screen for eligibility. Paper copies of the eligibility criteria (pathology reports, laboratory results, etc.) will be kept in the shadow charts by the study coordinator. The shadow charts will be kept in a secure, locked area. Clinical data will be tracked in Oncore. Other data, such as treatment planning images, will be maintained on a password protected computer located in the Department of Radiation Oncology on a secured server.

Response Criteria
Response will be assessed using tumor measurements (longest dimension) obtained from MRI and/or CT with or without contrast, documentation of presence of metastatic disease, results of post-treatment pathology (if available).
Definitions of response:

- Stable – no change
- Progressive Disease – 20% or more increase in sum of diameters of the target lesion. The sum must also demonstrate an absolute increase of 5 mm or more or the presence of a new lesion or lesions.
- Partial Response - At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters**.**
- Complete Response – no visible target lesions
- Pathological Complete Response – Based on increase or decrease of available biopsy results

13.0 REFERENCES

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Appendix I.

It is important to note that dose to the normal tissues surrounding the target has not been allowed to dose escalate. Tolerance levels selected for these normal organs (see Table I. and Appendix I., are consistent with RTOG standards and normal tissue limits approved for UHCMC Protocol Case 13807 associated with Prostate Cancer with Cyberknife irradiation.

Table I. Dose Specifications for Normal Organs (and Appendix I.)

6. Bowel – No more than 1 cc can receive 8 Gy/fx for a total of 24 Gy in 3 to 4 fractions.
7. Cord – No more than 0.3 cc can receive 6.7 Gy/fx for a total of 20 Gy in 3 to 4 fractions.
8. Stomach - No more than 1.0 cc can receive 7.3 Gy/fx for a total of 22 Gy in 3 to 4 fractions.
9. Liver – No more than 2/3 of liver volume can receive 5.7 Gy/fx for a total of 17 Gy in 3 to 4 fractions. Additionally within that volume – 800 cc should not receive more than 5.0 Gy/fx for a total of 15 Gy in 3 to 4 fractions.
10. Contralateral Kidney- No more than 5 % of the volume can receive more than 4.7 Gy/fx for a total of 14 Gy in 3 to 4 fractions.