UT SOUTHWESTERN
Harold C. Simmons Cancer Center

PROTOCOL NUMBER: STU 122013-030
A Phase II Trial of Stereotactic Ablative Radiation Therapy (SABR) for patients with primary Renal Cell Cancer (RCC)

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.
Version #9

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Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

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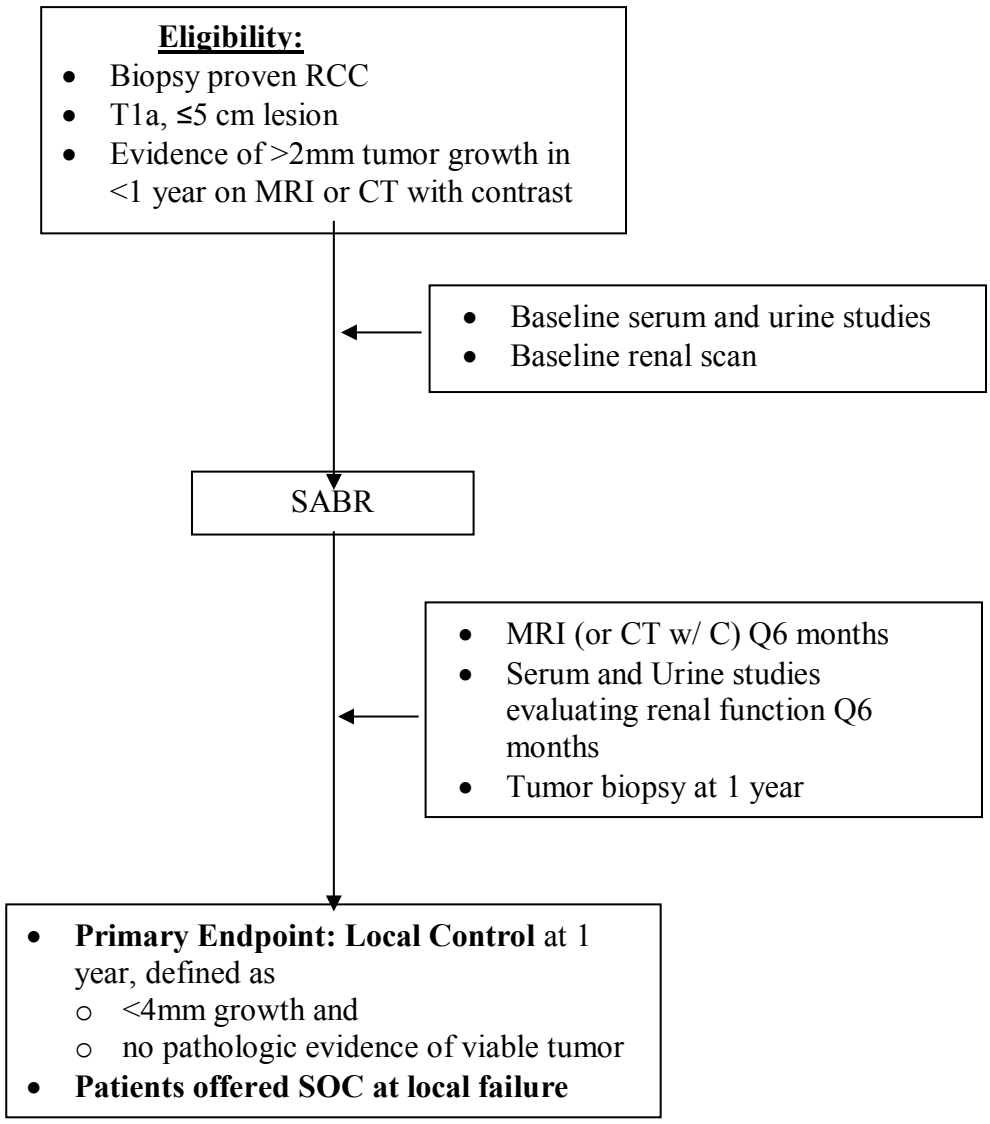
LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AS	Active Surveillance
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DOT	Disease Oriented Team
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IHC	Immunohistochemistry
IV (or iv)	Intravenously
MRI	Magnetic Resonance Imaging
NSS	Nephron Sparing Surgery
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
pCR	Pathologic Complete Response
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
p.o.	peros/by mouth/orally
PR	Partial Response
RCC	Renal Cell Cancer
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SABR	Stereotactic Ablative Radiation Therapy
SBRT	Stereotactic Body Radiation Therapy
SRM	Small Renal Mass
SCCC	Simmons Comprehensive Cancer Center
SD	Stable Disease

SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	Stereotactic Ablative Radiation Therapy (SABR) for patients with primary Renal Cancer (RCC)
Short Title	SABR for primary RCC
Protocol Number	The standard protocol number used to identify this study
Phase	Phase II
Methodology	Single arm open label
Study Duration	5 years
Study Center(s)	Single-center
Objectives	To eliminate growth and viable tumor in biopsy proven small primary RCC by SABR
Number of Subjects	16
Diagnosis and Main Inclusion Criteria	biopsy proven and growing small primary RCC
Study Product(s), Dose, Route, Regimen	Stereotactic Ablative Radiation Therapy (SABR): 3 fractions of 12Gy, or 4 fractions of 10Gy or 5 fractions of 8 Gy
Duration of administration	1-3 Weeks.
Reference therapy	Lesion growth is being compared to pre-treatment growth
Statistical Methodology	Exact binomial test

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

The incidence of kidney cancers has been on the steady rise since 2004 with a rise of 4.1% per year [1]. In 2012 an estimated 64,770 cases diagnosed and 13,570 deaths occurred due to kidney cancers, the majority (92%) of which were renal cell cancers (RCC) [1]. This places kidney cancers within the ten highest cancers in terms of incidence as well as death. More than half of these cases were diagnosed at the local stage. The common use of ultrasound, computed tomography, and magnetic resonance imaging resulted in an increase in the incidental discovery of small renal tumors (<4 cm) [2, 3]. Surgery remains the mainstay of curative treatment for renal cell carcinomas. However, depending on patient health status and tumor size, observation and in situ tumor ablation are alternatives. The objective of surgery is to excise all tumors with an adequate normal tissue margin [2]. As such, nephron-sparing surgery (NSS), primarily in the form of partial nephrectomy, is commonly utilized as a treatment for small renal tumors. Accepted indications for NSS include presence of a solitary kidney, reduced renal function, and medical conditions with future risk for reduced renal function [4-7]. In fact, multiple studies have shown that partial nephrectomy achieved similar results when compared to radical nephrectomy in properly selected patients [4-11]. In an effort to provide the advantages of NSS while reducing its morbidity, laparoscopic and robotic partial nephrectomy has been developed [12, 13].

Ablative treatments for renal cell carcinoma, although not completely non-invasive, are currently being developed that further reduce the morbidity associated with NSS. Cryoablation and radiofrequency ablation (RFA) comprise the ablative modalities that are in clinical use [9, 14-20]. In all cases, kidney tumors are biopsied prior to or after ablation for histologic diagnosis. Unfortunately, the long-term oncologic efficacy of the ablative technologies remains unknown and no published study has reported rates of cancer-specific death, metastatic progression, or local disease recurrence after presumed successful ablation.

Conventional radiotherapy has not been used to treat primary renal tumors. Many technical challenges associated with treatment of kidney tumors including limited radiation tolerance of the normal kidneys and the surrounding tissues and difficulty of target localization have prevented routine use of radiotherapy for tumors of the kidney. However, the advent of image guided stereotactic radiosurgery system, which is completely non-invasive, has made feasible what was once technically prohibitive. Stereotactic radiosurgery has been used successfully to treat tumors of various anatomic sites including the brain, the liver, and the lung [21-23].

1.2 Stereotactic Ablative Body Radiation (SABR)

Stereotactic ablative radiation therapy (SABR) also known as Stereotactic Body Radiation Therapy (SABR) is an emerging treatment paradigm defined in the American Society of Therapeutic Radiology and Oncology guidelines as a “treatment method to deliver a high dose of radiation to the target, utilizing either a single dose or a small number of fractions with a high degree of precision within the body” [24] . Potential indications for SABR include a broad spectrum of tumor types and locations. The safety and efficacy of SABR to multiple sites is excellent as documented in multiple studies [25-27].

The concept of stereotactic radiosurgery involves tightly conforming dose of therapeutic radiation confined to a small region of the body. This results in eradication or ablation of the target tumor with sparing of surrounding normal tissues. The largest experience with stereotactic radiosurgery is for the treatment of intracranial tumors. This requires a rigid immobilization device, which often is directly attached to the bony skull. Until recently,

fractionated extracranial stereotactic radiosurgery has not been possible due to many technical challenges. The critical issues include accuracy of targeting the tumor, required rapid dose fall-off away from the tumor, and adjustment for target movement during the therapy. These factors could not be addressed simultaneously until the advent of stereotactic body radiotherapy.

There are several options for delivery of stereotactic radiotherapy dose to the target volume including TrueBeam, Cyberknife and Vero. The treatment machines have several factors in common. They are able to deliver the intended dose utilizing high energy (>4 MV) X-ray photons with accurate and reproducible treatment set up. The modern linear accelerator has been successfully used to deliver stereotactic radiotherapy. A landmark study by Timmerman, et al., reported a complete response rate of 27% for patients with in-operable non-small cell lung cancer after stereotactic radiotherapy with modern linear accelerator [28]. The stereotactic body radiotherapy is not limited to any particular machine. What is critical is the ability to deliver high dose accurately and safely.

The immobilization of the patient to minimize the movement of the target organ is also an important requirement during the stereotactic radiotherapy treatment. Stereotactic radiotherapy allows rapid reduction in the delivered dose away from the target bed. This is accomplished by utilizing multiple beams to converge on the target from various coordinates. In addition, the system must allow monitoring of the target via the direct imaging of the target itself with cone-beam CT (CBCT). The combination of tightly conforming dose to the intended target as well as verification of the target position during the treatment spares significant portion of the normal tissue from high dose radiotherapy. The real time tracking of the target position and stereotactic delivery of high dose to the target have not been possible until the advent of the stereotactic treatment system.

1.3 Rationale

SABR has been implemented successfully in the definitive management of many cancers including in the definitive setting of primary lung and prostate cancers [28-31] and currently under investigation in many other sites including breast, pancreas and liver [32-36]. In the metastatic setting, SABR has been successfully applied to the local control of metastatic lesions in multiple organ sites including CNS, lung, liver, pancreas, prostate and bone [32, 37-39]. In renal cancers, SABR has shown efficacy ranges of 90-100% and 82-95% for CNS and extra-CNS metastasis respectively [40-44].

Despite the extensive and growing experience with SABR in multiple cancer sites, its application to primary renal cancers has been limited to few retrospective reviews and two phase I studies [45, 46]. The first retrospective study by Dr. Beitler's group reported treating 9 patients treated to primary tumors in the kidney ranged from 1.5cm-10cm with a median follow up of 27 months[45]. He reported 4/9 patients to be alive with all survivers having tumor sizes <3.4 cm. Their dose was 40Gy in five fractions. Only two patients experienced nausea/vomiting and no other toxicity was reported. A second retrospective study reported in ASTRO 2004 from Cabrini medical center reported treatment of 33 primary renal lesions with a local control of 94% at median follow up of 17 months (Gilson et. al. 2004). In the Karolinska Institute experience, 8 patients received SABR to primary RCC with 8Gy x5 or 10Gy x3 [46]. At 4 year follow up five patients were alive with no recurrence and one patient had a local failure at 15 months with. Median survival was 58 months. They reported no changes in creatinine levels after SABR and no toxicity. Karolinska institute followed this report with the publication of a prospective phase II study of RCC patients that treated 10 patients with primary RCC with an overall survival (OS) of 32 months and 96% grade I and grade II toxicity [47]. Lastly, a phase I dose escalation study that enrolled 15 patients at Boston has been presented in the 2013 ASTRO meeting (Kaplan et. al. 2013) that examined dose levels of 7 Gy x 3, 9 Gy x 3, 11 Gy x 3, 13 Gy x3, and 16 Gy x 3. They reported two

failures in the lower 7 and 9 Gy dose levels only. The toxicities were two patients having acute grade 1 nausea, five experiencing acute grade 1 fatigue and one patient having late grade 3 renal dysfunction.

Radiation induced renal complications can be slow and non-inflammatory. The extent of radiation induced kidney damage is related to the volume of renal parenchyma receiving radiotherapy, total dose given to the kidney, dose per treatment, and other underlying medical conditions such as diabetes and hypertension. Acute radiation nephritis can be seen months after exposure to radiotherapy [48]. The clinical symptoms related to acute radiation nephritis include hypertension, edema, proteinuria, anemia, and uremia. In standard fractionated treatment to both kidneys about 50% of the patients will develop the clinical manifestation described above a dose of 23 Gy [49]. Among the clinical symptoms, the development of hypertension is the most important prognostic sign correlated with severe morbidity and death. However, when 50% or less of a single kidney is irradiated to a high dose (>26 Gy), clinical radiation induced nephropathy is rare [49].

In this phase II trial, the volume of high dose radiotherapy (>10 Gy) will be restricted to <50% of the entire kidney. The current study will also implement fractionated stereotactic radiosurgery to treat a unilateral kidney tumor. Fractionated radiotherapy is advocated to further reduce the potential toxicity arising from a large single fraction regimen. In fact, fractionated radiotherapy has been the standard treatment for many tumors in variety of locations to reduce the toxicity associated with radiotherapy. A fractionated stereotactic regimen has the potential to reduce the normal tissue toxicity that often accompanies radiotherapy.

Successful implementation of stereotactic radiosurgery of renal tumors may become an effective and the least invasive treatment modality. This study will refine the current understanding of the image guided conformal therapy to the kidney using stereotactic body radiotherapy.

Based on the published retrospective and the two prospective phase I trials, the dose fractionations evaluated in this trial is 8Gy x5, 10Gy x 4 and 12 Gy x 3. In a retrospective study published paper by Wersäll, et al, from the Karolinska Hospital, 50 patients with kidney cancer, both primary and metastatic, were retrospectively analyzed [50]. High rates of local control were achieved with doses ranging from 25 Gy to 45 Gy. The most common doses used were 40 Gy in 5 fractions and 45 Gy in 3 fractions. Another retrospective study used the dose of 40Gy in 5 fractions and both studies reported excellent control rate [45]. Therefore 8Gy x 5 is evaluated in this study. The 4 and 3 fraction equivalent doses to this dose levels are 10Gy and 12 Gy respectively, which are the two other dose levels included in this trial. Justification of the three fraction dose equivalent of 12Gy x 3 comes from the phase I study that did not see any failures at this level.

The study population for this trial is patients with biopsy proven primary RCC that are candidates for active surveillance (AS). Keeping patient safety in perspective, it is reasonable to offer an experimental treatment such as this to a patient population that would have otherwise been put in AS. At any sign of progression, the patients that have undergone SABR in this trial will be offered the standard of care (SOC) of radical nephrectomy, partial nephrectomy or ablation as deemed appropriate by the treating urologist—which is same as what would have been offered to them had they been in AS. The AUA defines AS patients to be those with small renal mass (SRM) with <3cm tumors. The NCCN recommends AS for patients with T1a tumors or tumors <4 cm. A number of retrospective and one prospective study reported on the natural history of SRMs [51-55]. A meta-analysis reviewed multiple retrospective studies and reported an average growth rate of 0.28 cm/year for these tumors [51]. They further reported a growth of 0.4 cm/year in the subset of patients that had biopsy confirmed RCC. Keeping clinical application in perspective, it is logical to use SABR only to tumors that are growing, since one third of the SRMs do not grow. Therefore, patients

showing growth >2mm in two scans will be enrolled and treated with SABR in this trial. The primary endpoint in this trial is local control and the hypothesis tested is that SABR to the SRMs will lead to an elimination of tumor growth. The local control will be defined using MRI or contrast CT and <4mm increase in single scan or <2.0mm increase in two different scans in the setting of an absence of radiographic indication of tumor viability will constitute local control [56]. Kidney function will be monitored closely to evaluate radiation induced kidney toxicity.

1.4 Correlative/Exploratory Studies

1.4.1 SABR induced immune response

Previous studies have demonstrated multiple immunogenic properties of radiation therapy (RT), especially when given at high doses such as with SABR [57, 58]. Since SABR is a highly focused therapy, it does not inherently immunocompromise the host. In addition, as opposed to conventional radiation fields, SABR is a highly focused therapy that spares the surrounding lymph nodes which are vital for an effective immune response. By not surgically removing the tumor, the body retains the antigen depot (dying tumor cells) within the host. Furthermore, since SABR causes local inflammation, dendritic cells (DCs) are attracted into the tumor. The antigen-presenting properties and the induction of immunogenic cell death by SABR are well documented [59]. SABR-induced tumor cell death is primarily via mitotic catastrophy or necrosis, both of which are known to be immunogenic cell deaths as opposed to apoptosis, which is immunologically tolarogenic [60]. *In vivo* studies have shown that radiation induces release of damage (or danger)-associated molecular patterns (DAMPs) such as HMGB1, HSP and calreticulin into the extracellular matrix and thereby promotes the recruitment and activation of antigen-presenting cells (APCs) such as DCs for antigen presentation [61-63]. Subsequently, the APCs migrate to the draining lymph nodes for the presentation of the antigens and efficiently present tumor antigens in the cell surface MHC molecules to T cells [64]. The T cells initiate an adaptive immune response resulting in antibody production and the expansion of cytotoxic T cells. These are delivered to both the primary and metastatic tumor sites. Increased trafficking of CD8+ T cells to both irradiated tumor and their draining lymph node has been demonstrated [64, 65]. Furthermore, RT causes a dose-dependent increase in MHC I tumor neo-antigen presentation by the tumor cells [66]. This, in conjunction with a demonstrated increase in FAS death receptors on the tumor cell surface in response to radiation, renders tumor cells particularly susceptible to CD8+ T cell-mediated cytotoxic attack [67, 68].

The correlative studies will explore the mechanisms of possible immune enhancement by SABR. Activation of each arm of the immune response will be evaluated separately utilizing different assays. The humoral response will be evaluated using ELISA to measure the titer of tumor-specific antibodies generated by SABR against tumor tissue collected from the respective patients and established human renal cancer cell line Caki-2 (clear cell) and ACHIN (adenocarcinoma). An overall increase in tumor antigen-specific antibody will be measured using immunoblotting with patient sera as a source of primary antibody.

Enhancements of increased cytotoxicity to renal cancer cells can be measured by cytotoxicity assays. Antibody-dependent cell-mediated cytotoxicity (ADCC) measures the cell-killing ability of certain lymphocytes that require the target cell to be marked by an antibody and thus measures the humeral response [69]. On the other hand, lymphocyte-mediated cytotoxicity assay will measure the formation of tumor-specific CTLs among the lymphocytes collected from patients with the controls being lymphocytes collected from the same patients before SABR. Since it is not practical or feasible to obtain sufficient quantities of tumor cells from each patients to assess a quantitative cytotoxicity by these assays, established allogenic human renal cancer cell line Caki-2 and ACHIN will be used for this purpose. It is a generally accepted principle of tumor immunology that there will be many common tumor antigens between different patient tumors of same site origin, and therefore tumor cell lines as well [69]. In fact, the tumor antigens (PSA, CEA, CA 19-9 etc.) that are in clinical practice are reported to be present in a significant portions

of patients of the respective tumor site. This concept of commonality of tumor antigens between allogenic tumor cell lines and patients is put into clinical practice by the GVAX anti-tumor vaccine which is currently in early phase clinical trials for pancreatic, melanoma and renal cancer [70, 71]. GVAX consists of multiple human tumor cell lines of the respective site, that is modified to express GM-CSF, and killed with radiation prior to injection in patients. The presence of common tumor antigens in the cell lines and patient's tumors, leads to induction of an immune response. The LNCaP and PC-3 cell lines has been shown to express many of the common renal cancer antigens, and therefore, is an appropriate surrogate to be used instead of patient's own cells and has been used in similar *in vitro* cytotoxicity assays [72-76].

Cytokines are hormonal messengers responsible for most of the effects in the immune system such as activation of innate versus adaptive immune response, cellular versus humeral immune response [77, 78]. For example, an increased level of IL-2 and IFN-γ suggests activation of Th1 cells leading to activation of macrophages and suggests a cell-mediated adaptive immune response whereas IL-4 and IL-5 may indicate Th2 activation and induction of humoral immunity [69, 78]. An increase in IL-17 may suggest activation of autoimmune responses [79]. Therefore, measurements of serum cytokine levels have generally been used previously in clinical trials as surrogates to assess specific activation of immune pathways [80, 81]. Serum cytokines from this clinical trial before and after SABR will be measured using an extensive array of cytokines to explore the specific immune pathways that are initiated by SABR. The planned array of cytokines will measure levels of the following cytokines before and after treatment for each patients: Th1/Th2/Th17 cytokines: IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12p70, IL-13, IL-17 TNF-α; pro-inflammatory cytokines: GM-CSF, IFN-γ, IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12p70, TNF-α; Chemokines: Eotaxin, MIP-1β, TARC, IP-10, IL-8, MCP-1, MCP-4, KC, and others including IL-6, IL-12, TGF-β and HMGB1.

Many surrogate markers for activated and proliferating lymphocytes have been described. Some of these markers include CD25, CD71, CD45RO, CD107a, CD54, CD69, Ki67 and ICOS/CD278 [82-85]. These markers are easily measured with antibodies specific for the markers that are tagged with a fluorophore utilizing FACS analysis. Also using FACS, activation markers on other immune cells such as CD80 and CD 86 on DCs, and inhibitory markers on monocytes such as PD-1 can be measured as surrogates of immune activation or inhibition. These measurements from PBMCs collected from patients before and after treatment will give us further information regarding the intensity of the immune response. Additionally, PD-L1, the ligand of PD-1, often expressed in tumor cells, can be quantified from patient pre-treatment tumor biopsy.

The relative levels of different monocyte subpopulations in the tumor biopsy sample after treatment as well as in the peripheral circulation often dictate the overall outcome of an immune response, and has been reported in previous immunotherapy trials [86]. Exploration of possible mechanisms of treatment failure can be explored from this analysis as well. Therefore, different subpopulation of monocytes and lymphocytes will be quantified in patient PBMCs (and in tumor biopsy samples where applicable) collected before and after treatment utilizing markers specific for those cells.

Many studies have suggested that imaging characteristics of tumor may be used to predict treatment outcome of radiation therapy for various tumors, such as lung [87], prostate[88], cervical[89]. By analyzing CT and MRI images on patient enrolled in this trial, we plan to explore whether image characteristics of CT and MRI acquired prior to the SBAR treatment, such as intensity features, texture features and geometry features, are correlated with the treatment outcome of SABR for RCC. Through analysis of the change of these image characteristics in the follow-up scans, we will also explore whether the change of these features can be used for early prediction of SABR treatment response.

Multiple clinical and pre-clinical studies have demonstrated the dependence of tumor radiation resistance with tumor hypoxia, including those performed in our institution [90-94]. Using a combination of blood oxygen level dependent (BOLD) and tissue Oxygen Level Dependent

(TOLD) MRI, accurate insight regarding tumor oxygenation can be obtained. In RCC, tumor hypoxia and its dependence on treatment outcome, specifically with SABR, has not been explored before. Therefore, BOLD and TOLD MRI sequences will be incorporated in the baseline and six month post-treatment scans for patients enrolled in this trial.

1.4.2 Tumor respiratory motion modeling

Respiratory motion causes significant geometric and dosimetric errors in the administration of stereotactic radiotherapy (SBRT) for renal cell cancer (RCC). The purpose of this study is to create and validate patient-specific motion models of the abdominal anatomy with high spatial and temporal resolution. These models will be used to develop novel four-dimensional (4D=3D+time) techniques for radiotherapy treatment planning and real-time motion-adaptive dose delivery.

This study will involve the acquisition of real-time optical surface monitoring data from human patients with primary lesions, following their 4D computed tomography scan (4DCT - standard-of-care at our clinic). These data will be to build a 4D motion model that describes the spatial location of each voxel in the CT volume as a function of time. In the treatment room, before dose delivery, the model will be updated and validated using three 15s long kV fluoroscopic sequences, each acquired from a different angle, and time-correlated with optical surface monitoring. The data and the findings of this study will be used solely for research and will not affect a patient's clinical treatment plan or dose delivery. The data acquired in this study will vastly improve our knowledge of how respiratory motion affects tumors and organs at risk within the abdominal anatomy and enable the development of better motion-managed radiation therapy paradigms that may help other patients with thoracic and abdominal cancers.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

2.1.1 To evaluate if SABR to SRMs is able to eliminate its growth and viable tumor.

2.2 Secondary Objectives

2.2.1 To describe the adverse events associated with the administration of SABR to SRMs

2.2.2 To measure the growth rate of SRMs after SABR treatment.

2.2.3 To measure the changes in kidney function, creatinine levels, renal perfusion and GFR after SABR treatment.

2.2.4 To measure tumor viability pathologically one year after SABR treatment with a biopsy.

2.2.5 To assess radiographic changes of the SRM after SABR treatment, including tumor viability, %enhancement, necrosis, T2 signal, tumor cellularity with diffusion-weighted imaging

2.2.6 To assess local, regional and systemic progression of disease after SABR to SRM

2.2.7 To assess time to progression (TTP) of disease from the first SABR treatment.

2.2.8 To assess progression free survival (PFS). PFS is defined as the length of time from start of treatment to the time of loco-regional disease progression (as defined in Section 2.4) or death from any cause.

2.2.9 To assess overall survival (OS). OS is defined as the duration of time from start of treatment to the time of death from any cause.

2.2.10 To assess tumor growth, local failure and indeterminate disease response (IDR) as defined in section 6.1.4

2.3 Exploratory Objectives

2.3.1 To evaluate the cytokine changes brought on by SABR to SRM and to evaluate generation of any immune response specific to tumor cells.
2.3.2 To evaluate whether radiographic spatial-temporal tumor features extracted from CT and MRI can be used to predict treatment response of tumor to SABR.
2.3.3 To evaluate if tumor oxygenation as measured by BOLD/TOLD MRI sequences is able to predict tumor response to SABR.
2.3.4 To model kidney and tumor motion with respect to respiration

2.4 Endpoints

2.4.1 Primary Endpoint:

Local control of the SRMs will be defined as <4mm increase in the longest tumor diameter compared to pre-treatment scan on an MRI or contrast-enhanced CT scan in the setting of no radiographic or pathologic evidence of viable tumor.

2.4.2 Secondary Endpoints:

2.4.2.1 Adverse Events: Acute and late adverse events will be assessed using NCI's CTCAE v4.0 toxicity criteria and RTOG/EORTC criteria (Appendix A and B).

2.4.2.2 Growth Rate: Growth of the longest diameter of the SRMs after SABR treatment will be compared to baseline and expressed as growth rate of cm/year.

2.4.2.3 Loco-regional and systemic progression: Loco-regional and systemic progressive disease will be defined based on local, regional and systemic progression as defined by AJCC (7^{th} edition) kidney cancer staging and any stage >T1a (>4cm) constitutes a progression.

2.4.2.4 Kidney function: To assess kidney function creatinine levels and renal perfusion scan will be performed at baseline and periodically after SABR (See section 5).

2.4.2.5 Radiographic changes: Radiographic changes of the SRM after SABR treatment will be assessed using MRI interpretation by a radiologist.

2.4.2.6 Tumor Growth, Local failure and Indeterminate Disease Response as defined in section 6.1.4

2.4.3 Exploratory Endpoint:

2.4.3.1 Immune Response: Immune response will be measured using ELISpot assay, T-cell proliferation assay, Immunoblot and ELISA.

2.4.3.2 Spatial-temporal radiographic tumor features predictive value: Predictive value of each feature for SABR treatment response will be assessed using the area under the receiver operating characteristic curve.

2.4.3.3 To develop a 4D model of patient-specific tumor motion

3.0 SUBJECT ELIGIBILITY

Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 Age ≥ 18 years.

3.1.2 Renal mass ≤ 5cm

3.1.2.1 The treating renal mass must be ≤ 5cm. Other renal masses (cysts etc.) of any size will not make the subject ineligible.

3.1.3 Biopsy proven Renal neoplasm
3.1.3.1 All histology of renal cancers are included, including oncocytoma

3.1.4 Growth of renal mass >2mm in radiographic scans must be demonstrated within a one year period.

3.1.5 Ability to understand and the willingness to sign a written informed consent.

3.1.6 Subject is able to undergo either an MRI or administration of contrast agent for CT.

3.1.7 Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) for the duration of the study. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.6.1 A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.2 Exclusion Criteria

3.2.1 Subject has received any treatment for the treating renal mass; such as RFA or cyroablation.
3.2.1.1 If other renal masses received RFA or cryoablation or surgery, then these patients are eligible.

3.2.2 Subjects received previous abdominal radiation

3.2.3 Evidence of Metastatic Disease, unless disease-free for ≥ 3 years prior to registration, (non-melanomatous skin cancer and in-situ cancers are okay).

3.2.4 Female subjects who are pregnant or planning to become pregnant during the course of SABR.

4.0 TREATMENT PLAN: Stereotactic Body Radiation Therapy

4.1 Definitions

Stereotactic body radiation therapy (SABR), also known as stereotactic ablative radiotherapy (SABR), is a treatment conduct used to deliver highly focused and accurate radiation dose to demarcated targets outside of the brain where the entire course of therapy for an individual target is delivered in few fractions (≤5, oligofractionation). SABR has been defined and its appropriate conduct extensively reviewed by several professional radiotherapy societies. For this protocol, we will maintain definitions of SABR from the ACR/ASTRO consensus and conduct from the same along with requirements laid out by the AAPM. When and if there is a discrepancy between these professional society guidelines and this protocol, the protocol should be followed.

4.1.1 Elements and Technologies of SABR

4.1.1.1 Secure Immobilization

With more dose per fraction being delivered and more emphasis on quality assurance of set-up and delivery, typical SABR treatment sessions are longer than with conventional radiotherapy. Accuracy of set-up must be assured throughout the duration of treatment. Controlling variables such as patient discomfort and unintended movements improves accuracy and allows for small uncertainty margins that would generally lead to more favorable dose distributions. Immobilization should focus on patient comfort as pain confounds accurate set-up. While historically immobilization with stereotactic radiotherapy involved rigid, fixed immobilization (typically to bone), modern extracranial stereotactic radiotherapy delivery involves employing large surface area of contact with molded cushions, body frames, etc., to distribute body weight more evenly. Laying patients on flat couches and relying solely on image-guidance for reproducible set-up is strongly discouraged.

4.1.1.2 Effective Delineation of Targets

The edge of the intended target should be distinct from uninvolved normal tissue such that there is little need for expansions for subclinical extension or uncertainty. A variety of appropriate imaging can be used to define targets clearly so long as these imaging platforms can be accurately and reliably “fused” with the planning data set and brought into the context of stereotactic targeting conveyed in the next paragraph. Patient’s baseline MRI will be fused to the planning CT (preferably with IV contrast if patient is able to tolerate) for this purpose whenever applicable.

4.1.1.3 Stereotactic Targeting

The term ‘stereotactic’ for the purposes of this protocol implies the targeting, planning, and directing of therapy using beams of radiation along any trajectory in 3-D space toward a target of known 3-D coordinates. The coordinate system is defined by reliable ‘fiducials’. A fiducial may be external or internal to the patient’s body. External fiducials may relate to a frame or treatment device. Internal fiducials may be implanted markers OR reliably identified anatomy including the tumor itself (e.g., acquiring tomographic views of the tumor simultaneously with the treatment). In all cases, the relationship between the fiducial and the actual tumor position in real time should be reliably understood for both planning and treatment. The coordinate system defined by the fiducials should be directly related to the radiation-producing device (e.g., couch and gantry) in a reproducible and secure fashion. Capability should exist to define the position of

targets within the patient according to this same 3-D coordinate system. As such, the patient is set up for each treatment with the intention of directing the radiation toward an isocenter or target according to the known 3-D coordinates as determined in the process of treatment planning.

4.1.1.4 Motion Assessment and Management

Motion assessment involves a query to appreciate the nature of both tumor target and normal tissue displacement that may occur during a typical SABR treatment session. Dynamic imaging is typically required for such an assessment such as fluoroscopy, ultrasound, 4-D CT, etc. It is not enough to understand how surrogates for targets move (e.g., the diaphragm for a lung tumor). Instead, the actual motion of the target must be reasonably understood. In turn, this assessment may either allow appropriate expansions of targets to encompass this movement (if the expansion would only be minimal) OR to trigger the use of motion control. Motion management is a logical reaction to excessive motion appreciated from the motion assessment where either the natural physiological motion is modified (e.g., dampened) or countered with an active process (e.g., gating or tracking).

4.1.1.5 Compact Dosimetry

There is no intention to perform adjuvant therapy for microscopic infiltration or involvement with SABR. It follows that while the target should be hit hard with radiation to disable cancer proliferation, uninvolved normal tissues should be likewise spared as much as possible. In striking contrast to radiotherapy given historically and conventionally where areas 'at risk' were bathed in small daily dose fractions, similar approach with SABR would be prohibited by late toxicity. Instead, dose outside the target should fall off rapidly in all directions to avoid such toxicity. Gradients may appropriately be even steeper next to critical serially functioning normal structures (ie, tubes and wires of the body).

4.1.1.6 Image Guidance

With such compact dosimetry delivering potent tumorical dose surrounding small to medium sized targets perhaps in association with critical normal structures, geometric errors in beam positioning could be catastrophic both in regard to tumor control and toxicity. Image guidance increases the confidence that beams are in alignment during dose delivery allowing reduction of margins that might otherwise be added for uncertainty.

4.2 SABR Dose Delivery

4.2.1 Treatment Sites

Treatment of primary tumors of the kidney will be allowed on this protocol.

4.2.2 Target Prescription Dose

SABR prescription dose will be delivered to the periphery of the planning target volume for each lesion treated. Investigators will have discretion in choosing from allowable dose levels from the table below. Treating physicians should choose their dose based on established planning guidelines at their center including their ability to respect normal tissue tolerance listed in the protocol. It is not required that all targets be treated with the same dose fractionation.

Allowed prescription dose:

Number of Fractions	Total Cumulative Dose Encompassing 95% of Planning Target Volume
3	36 Gy
4	40 Gy

5	40 Gy

4.2.3 Treatment Timing and Duration

For a given lesion (target), a minimum of 40 hours and a maximum of 8 days should separate consecutive treatments. All treatment must be completed within 21 days.

4.2.4 Daily Treatment

Ample time should be scheduled for each treatment to insure careful execution of the SABR for the lesion. Avoid long treatment sessions as the resulting discomfort for the patient from prolonged immobilization may confound accuracy.

4.2.4.1 Daily Image Guidance

Appropriate SABR includes more sophisticated image guidance to reduce uncertainties and allow smaller treatment margins. Confidently identifying the stereotactic fiducials (e.g., implanted markers, close body tissue surrogates, or even the tumor itself) before and during treatment mostly eliminates interfraction error and reduces intrafraction error allowing the smaller margins critical to the overall SABR approach.

4.3 SABR Technical Factors

4.3.1 Physical Factors and Treatment Platforms

Only photon (x-ray) beams produced by linear accelerators with photon energies of 4-10 MV will be allowed. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed. Photon beam energies > 10 MV but < 18 MV will be allowed only for a limited number (≤50% of all beams or all beam angles) beams that must travel more than a cumulative distance of 10 cm through soft tissue (not lung) to reach the isocenter OR a shorter distance if the tumor abuts the chest or abdominal wall (i.e., to spare skin dose).

Most commercially available photon producing treatment units are allowed except the exclusions noted above. As such, conventional linear accelerators, specialized linear accelerators with image guidance (e.g., Novalis, True Beam, Agility, Artiste, etc.) are allowed. These units can be used with conformal dose delivery or IMRT. Specialized dose painting accelerators (e.g., Cyberknife, or Tomotherapy) are allowed provided they meet the technical specifications of the protocol.

4.3.2 Minimum Field Aperture (Field Size) Dimension

Because of uncertainties in beam commissioning resulting from electronic disequilibrium within small beam apertures, an equivalent square field dimension of 3.0 cm is required for any field used for treatment delivery for sites using standard 3-D conformal techniques where nearly all of the PTV is encompassed for each beam. It is understood that this may exceed the technical requirements for small lesions [< 2.0 cm axial gross tumor volume (GTV) dimension or < 1.0 cm craniocaudal GTV dimension]. In such cases, the prescription dose is still prescribed to the edge of the defined planning treatment volume (PTV). For sites using dose painting including IMRT techniques (e.g., Cyberknife, Tomotherapy, etc.) where by design the entire PTV is not encompassed for each beam, smaller beam apertures are allowed. In addition, if the site has specifically commissioned the beams employed in credentialing and treatment to be applicable to smaller field sizes, they may reduce the minimum field aperture requirement to the size commissioned provided they provide documentation of such commissioning and get pre-approval by the physics co-PI for the study.

4.3.3 The Use of Intensity Modulated Radiation Therapy (IMRT)

The protocol allows for IMRT provided the site is credentialed for IMRT and SABR. However, SABR is, in general, a 3-D conformal treatment. Indeed, IMRT can result in dosimetric

inaccuracies especially in circumstances where tumor motion is either unknown or not properly accounted. Some platforms inherently use IMRT and must pass credentialing where motion is incorporated correctly (e.g., Tomotherapy). When using other platforms, IMRT is generally discouraged. When required for successful compliance, IMRT should only be utilized if tumor motion is less than 5 mm (e.g., confirmed inherently with free breathing or with abdominal compression), OR if motion control effectively diminishes motion effects (e.g., gating, breath hold, or tracking) below 5mm.

4.4 Localization, Simulation, and Immobilization

4.4.1 Patient Positioning

Patients will be positioned in a stable position capable of allowing accurate reproducibility of the target positions from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be used, including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients' external contours) with reference to the stereotactic coordinate system. Patient immobilization must be reliable enough to insure that the gross tumor volume (GTV) does not deviate beyond the confines of the planning treatment volume (PTV) with any significant probability (i.e., < 5%) during the treatment.

4.4.2 Assessment of the Magnitude of Internal Organ Motion

Special considerations must be made to account for the effect of internal organ motion (e.g., primarily breathing associated motion but also bowel peristalsis motion) on target positioning and reproducibility. As a first step, it is required that each site quantify the specific motion of a target so as to determine if management strategies listed in the next section are required to meet protocol guidelines. The GTV to PTV expansion limits, as defined below, are no greater than 0.5 cm in the axial plane and 1.0 cm in the craniocaudal plane. If tumor motion combined with set-up error causes any PTV to be greater than the GTV beyond these limits, then a motion management strategy (or plan to reduce setup error) must be employed with validation of success. Patient should be instructed to be in normal free breathing at time of initial tumor motion assessment. Deep inspiration or expiration breath hold is not allowed for initial tumor motion assessment as such assessment generally overestimates free breathing tumor motion. Options for motion assessment included real time fluoroscopy, 4-D CT scanning, or other methods approved by the study team.

4.4.3 Management of the Effects of Internal Organ Motion

In some tumor locations, assessed tumor motion measurement indicates that tumor motion would exceed the required small tumor expansions per this protocol (resulting in marginal miss or excessive volume of irradiation) unless a motion management strategy is employed. Acceptable maneuvers for motion management include reliable abdominal compression, accelerator beam gating with the respiratory cycle, tumor tracking, and active breath-holding techniques or other methods approved by the study committee. Internal organ management maneuvers must be reliable enough to insure that the GTV does not deviate beyond the confines of the PTV with any significant probability (i.e., < 5%).

4.4.4 Localization

Isocenter or reference point port localization imaging (anterior/posterior and lateral) for each separate lesion should be obtained at each treatment on the treatment unit (or patients should undergo a tomographic imaging study using the linear accelerator couch, if available) immediately before treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields for each lesion. All IGRT systems must be checked daily to guarantee coincidence between the imaging coordinate system and the treatment coordinate system. This test is required by the AAPM Task Group 142 report and is described in detail in both the ASTRO/ACR practice guideline on SABR available at:

http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/ro/stereo_body_radiation

and the ACR Technical Standard on IGRT available at:

http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/med_phys/monitor_IGRT.

This test is particularly important when the treatment equipment is not equipped with any device that allows direct visualization of anatomical structures using the treatment beam. For example, this test must be performed routinely for the CyberKnife, Tomotherapy units as well as any BrainLab equipment that does not include an electronic portal imaging device (EPID) that intercepts the treatment beam.

4.4.5 Isocenter and Lesion

Isocentric beam delivery platforms are commonly used in radiotherapy (e.g., the common gantry-mounted linear accelerator). For a given lesion where the isocenter is purposely placed at the geometric center of the target, isocentric setup allows accurate delivery, particularly with image-guidance, even in the presence of whole body rotational setup errors. However, for these same platforms when treating to an isocenter apart from the target, considerable targeting error is introduced due to rotations. As such, it is generally required that the lesion has an isocenter located in the center of the lesion for such platforms. In addition, some platforms, including the Cyberknife and Tomotherapy, are inherently non-isocentric. These platforms take special account in the setup and treatment process to rigorously detect and account for rotations to avoid errors.

4.5 Treatment Planning/Target Volumes

4.5.1 Image Acquisition

Computed tomography will be the primary image platform for targeting and treatment planning. The planning CT scans must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting and should ideally be done with IV contrast unless the patient has allergic problems with contrast or has renal insufficiency. Contrast will allow better distinction between tumor or other normal anatomy. Axial acquisitions with gantry 0 degrees will be required with spacing ≤ 3.0 mm between scans. Images will be transferred to the treatment planning computers via direct lines, disc, or tape.

4.5.2 Targets

The targeted lesion will be outlined and/or approved by an appropriately trained radiation oncology physician and designated the gross tumor volume (GTV). Kidney lesion will be drawn with appropriate CT windowing, contrast, and with the information from fusion of MRI in delineating tumor from normal tissue. **GTV targets will not be enlarged whatsoever for prophylactic treatment (including no "margin" for presumed microscopic extension); rather, include only abnormal imaging signal consistent with gross tumor (i.e., the GTV and the clinical target volume [CTV] are identical)**. An additional 0.5 cm in the axial plane and 1.0 cm in the longitudinal plane (craniocaudal) will be added to the GTV to constitute the PTV.

As an alternative, sites equipped with 4-D CT scanning equipment may generate an Internal Target Volume (ITV) using the inspiration and expiration images or maximum/minimum intensity projections (MIP/MinIP) as appropriate. Sites should be aware that the MIP reconstruction for lung or MinIP reconstructions for liver may erroneously define an ITV in cases of significant irregular breathing or when tumors abut soft tissue structures (e.g., the diaphragm for MIP) or fat (for the MinIP). The 4-D scan acquired for planning, however, should be obtained after initial assessment of tumor motion confirming that the tumor motion will be no greater than

0.5 cm in the axial plane and 1.0 cm in the craniocaudal plane. An ITV should NOT be defined by the merger of a deep inspiration CT scan and a deep expiration CT scan as such would typically overestimate tumor motion. The ITV, then, is generated using a CT dataset where motion control/management maneuvers are already successfully employed. This ITV can be expanded by the institution's geometric set-up uncertainty (e.g., 4-5 mm) to generate the PTV.

As an example of this process, an experienced RTOG institution employs the following steps to assess motion, manage motion, acquire image datasets, and generated targets for lung targets. First a motion study is done (using fluoroscopy) to determine if the GTV is moving more than 1.0 cm. If it is, abdominal compression is applied with coaching (e.g., urging the patient not to "push back" against the abdominal plate) until the GTV moves less than 1.0 cm (verified again on fluoroscopy). Then, with compression/coaching applied when necessary, a 4-D CT is done. The 4-D CT at 2 mm slice spacing allows the site to generate an ITV using either by a reconstructed MIP or with the expiratory/inspiratory phase scans, but this is a motion managed ITV (not necessarily free breathing). The site confirms that this motion managed ITV generated by the 4DCT (as opposed to the fluoroscopy assessment) has limited GTV motion per protocol requirements. As the site treats in a stereotactic body frame, the validated institutional setup error is small. The site compares the mid amplitude GTV expanded by 0.5-1.0 cm PTV as required by protocol requirements to the ITV plus setup error to insure they are consistent. The resulting PTV is small yet contains tumor motion and all setup errors.

4.5.3 Dosimetry

Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each lesion to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are preferable. Typically, ≥ 10 static beams of radiation will be used with roughly equal weighting. Generally, more beams are used for larger lesion sizes. When static beams are used, a minimum of seven non-opposing beams should be used. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized. For this protocol, when using a gantry mounted linear accelerator, the isocenter is defined as the common point of gantry and couch rotation for the treatment unit. For other types of treatment units (e.g., Tomotherapy or CyberKnife), a reference point in space that is typically positioned at the center of the target is used instead of a mechanical isocenter. For non-IMRT or dose painting techniques, the conformal field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). The only exception will be when observing the minimum field dimension of 3 cm when treating small lesions (see above). As such, prescription lines covering the PTV will typically be the 60-90% line (rather than 95-100% as is common with conventional radiotherapy). Higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. The stereotactic reference point (corresponding to the mechanical isocenter for gantry mounted treatment units) will be determined from system fiducials (or directly from the tumor) and translated to the treatment record.

In contrast to conventional radiotherapy planning, there is no inherent desire or intent for achieving dose homogeneity within a target for an SABR treatment plan. Rather than prioritizing target dose homogeneity, SABR treatment planning prioritizes adequate minimum target coverage and rapid dose fall-off gradients outside of the target. Hot spots within targets (inhomogeneity) are generally accepted without consequence since targets are mostly tumor. In the case, however, of a PTV intersection with an adjacent serially functioning named normal structure (e.g., the esophagus), measures will be taken to avoid hot spots specifically in the intersecting normal structures as will be described in later sections.

4.5.3.1 Normalization

The treatment dose plan for each lesion treated will be made up of multiple static beams or arcs as described above. For both IMRT and CyberKnife treatments, the apertures are determined by inverse treatment planning. The plan should be normalized to a defined point corresponding closely to the center-of-mass of the PTV (COMPTV). This normalization is used to

select the isodose surface surrounding the target (see below where the exact coverage is stated as 95% of the PTV). Typically, in the case of the gantry mounted treatment units, this point will be the isocenter of the beam rotation; however, it is not a protocol requirement for this point to be the isocenter. For treatment units that do not have a mechanical isocenter, the center-of-mass of the PTV should be used.

Regardless of the treatment unit type, the point identified as COMPTV must have defined stereotactic coordinates and must receive 100% of the normalized dose. Because the beam apertures for the 3D-CRT approach coincide nearly directly with the edge of the PTV (little or no added margin), the external border of the PTV will be covered by a lower isodose surface than usually used in conventional radiotherapy planning, typically around 80% but ranging from 60-90%. For the treatment techniques that use inverse planning algorithms, this same isodose coverage must be achieved. The prescription dose will be delivered to the margin of the PTV (as defined below) and fulfill the requirements below. As such, a “hotspot” will exist within the PTV centrally at the COMPTV with a magnitude of the prescription dose times the reciprocal of the chosen prescription isodose line (i.e., 60-90%).

4.5.3.2 Tissue Density Correction (Tissue Heterogeneity)

For purposes of dose planning and calculation of monitor units for actual treatment, approved corrections for tissue heterogeneity must be used. Examples of appropriate tissue density heterogeneity correction algorithms include properly commissioned superposition/convolution (collapsed cone), AAA, and Monte Carlo. Simple pencil beam and Clarkson algorithms that account for attenuation but not scatter will not be allowed.

4.5.3.3 Composite Planning Dosimetry

While a successful strategy of iterative treatment planning on a per lesion basis is typically carried out in practice when optimizing dosimetry, overall treatment appropriateness and compliance will be judged based on the composite treatment plan summarizing the effects of all beams to all lesions treated simultaneously in absolute (not percentage) dose. This is required even if different lesions are treated on different days. Only composite plans will be submitted for quality assurance. An exemption will be if large (more than 40 cm) cranio-caudal distances separate two adjacent lesions where scanning a common dataset for planning might be problematic (e.g., tube over-heating). In this case, two separate planning data sets will be submitted without a composite plan.

4.5.3.4 Successful Treatment Planning

Successful treatment planning **for each lesion treated** will require accomplishment of all 7 of the following criteria:

1. Normalization

The treatment plan should be normalized such that 100% corresponds to the center of mass of the PTV (COMPTV) receiving the highest dose on protocol.

2. Prescription Isodose Surface Coverage

The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface selected for that lesion and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose selected for that lesion.

3. Target Dose Heterogeneity

The prescription isodose surface selected in number 2 (above) must be ≥ 60% of the dose at the center of mass of the PTV (COMPTV) and ≤ 90% of the dose at the center of mass of the PTV (COMPTV). The COMPTV corresponds to the normalization point (100%) of the plan as noted in number 1 above.

4. High Dose Spillage

a) Location: Any dose > 105% of the prescription dose selected for that lesion should occur primarily within the PTV itself and not within the normal tissues outside the PTV. In addition for the PTV receiving the highest dose in the plan, the cumulative volume of all tissue outside the PTV receiving a dose > 105% of the highest prescription dose should be no more than 15% of

the size of the PTV volume receiving the highest dose.
b) Volume: Conformality of PTV coverage will be judged such that the ratio of the volume of the prescription isodose meeting criteria 1 through 4 to the volume of the PTV is ideally < 1.2. These criteria will not be required to be met in treating very small tumors (< 2.0 cm axial GTV dimension or < 1.0 cm craniocaudal GTV dimension) in which the required minimum field size of 3.0 cm results in the inability to meet a conformality ratio of 1.2.
5. Intermediate Dose Spillage
The falloff gradient beyond the each PTV extending into normal tissue structures must be rapid in all directions and meet the following criteria:
a) Location: The maximum total dose over all 3 fractions in Gray (Gy) to any point 2 cm or greater away from the PTV in any direction must be no greater than D2cm where D2cm is given by the tables below.
b) Volume: The ratio of the volume of the 50% isodose volume (50% of the prescription dose for the treated lesion) to the volume of the PTV must be no greater than R50% where R50% is given by the table below.

Ratio of 50% Isodose Volume to the PTV, R50%		Maximum Dose at 2 cm from PTV in any direction as % of prescribed dose (PxD). D2cm (Gy) = % x PxD		PTV Volume (cc)
Deviation		Deviation		
none	acceptable	none	acceptable	
<5.9	<7.5	<50.0	<57.0	1.8
<5.5	<6.5	<50.0	<57.0	3.8
<5.1	<6.0	<50.0	<58.0	7.4
<4.7	<5.8	<50.0	<58.0	13.2
<4.5	<5.5	<54.0	<63.0	22.0
<4.3	<5.3	<58.0	<68.0	34.0
<4.0	<5.0	<62.0	<77.0	50.0
<3.5	<4.8	<66.0	<86.0	70.0
<3.3	<4.4	<70.0	<89.0	95.0
<3.1	<4.0	<73.0	<91.0	126.0
<2.9	<3.7	<77.0	<94.0	163.0

Note 1: For values of PTV dimension or volume not specified, linear interpolation between table entries is required.
Note 2: Institutions are encouraged to stay within the values listed as “none” in the table above so that the treatment plan is considered to be per protocol. It is recognized that some treatment planning situations might be more challenging and fall outside these limits, so staying within the values listed as “acceptable” is also permitted. Protocol deviations greater than listed here as “acceptable” will be classified as “unacceptable” for protocol compliance.
Note 3: For tumors within 2 cm of the skin, it may be difficult to meet the values for D2cm and R50. In these cases, these criteria will not be used.

6. Adherence to Critical Organ Dose-Volume Limits
Attempts should be made to meet or be better than the normal tissue constraints listed below while observing the treatment planning priorities listed in Section 5.7.
7. Conducting planning with respect to the planning priorities (Section 5.7)

4.6 Planning Priorities

4.6.1 Overall Strategies

Successful treatment planning criteria are listed in the previous section. In general, attempts should be made to successfully satisfy all of the criteria without deviation. In some circumstances, improvements can be made to the dosimetry plan beyond simply meeting the specified goals. In other circumstances, clinicians are faced with the prospect of not ideally meeting one or more of the criteria (i.e., accepting an acceptable deviation). In this section, we provide priorities in which a most ideal plan for protocol purposes is realized. Suggested priority of planning goals in order of importance is:

1. Respect spinal cord, cauda equine and sacral plexus dose constraints.

2. Meet dose "compactness" constraints including the prescription isodose surface coverage, high dose spillage (location and volume), and intermediate dose spillage (D2cm, and R50) as these define the "essence" of SABR.

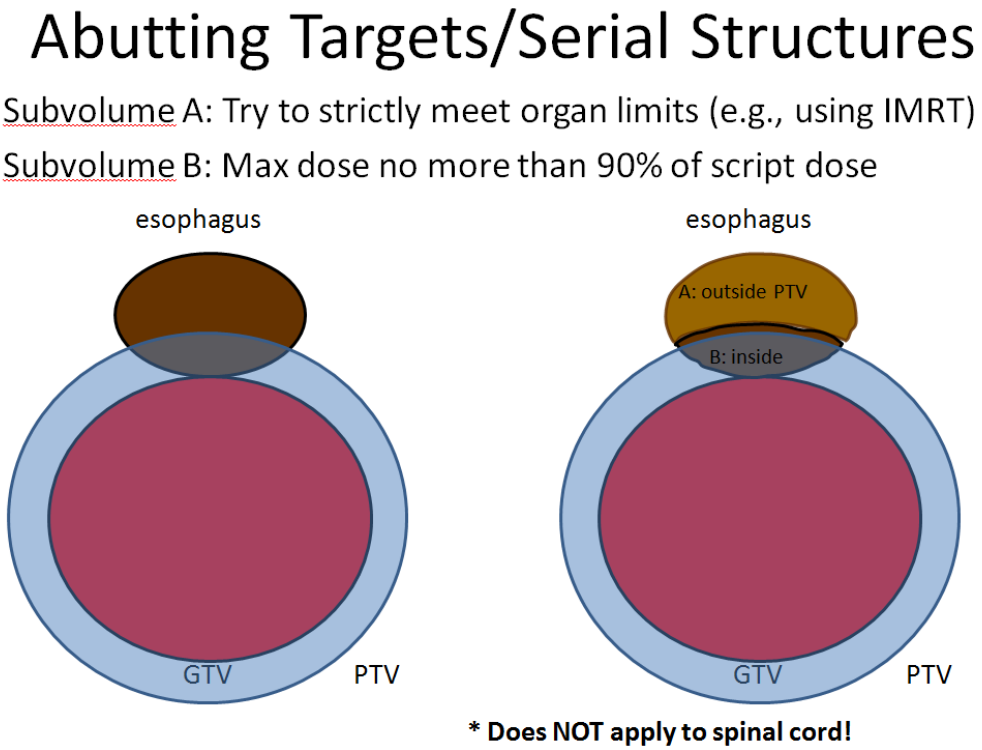
3. Meet critical structure constraints other than those listed in 1.

The organ constraints are last in priority (except for nervous system tolerance), because they are the least validated. The "essence" of a stereotactic plan is captured mostly in the dose compactness justifying their higher priority. As an example in a case where not all goals can be met, it would be suggested to meet dose compactness goals without deviation even at the expense of a non-spinal cord normal tissue having acceptable deviation. Unacceptable deviations should be avoided in all cases. Again, these are suggested planning priorities and clinicians must use their judgment and experience in actual treatment given the variability of patient presentation and tolerance.

As an example, in some cases a target abuts a normal tissue structure with an assigned constraint. Obviously, it would be impossible to utilize the required expansions, treat to 54 Gy PTV dose, and also meet the normal tissues maximum dose constraint. With the exception of the spinal cord, the protocol allows an "acceptable" deviation such that the abutting normal tissue is allowed a maximum point dose of 105% of the prescription dose; however, the volume constraint must still be respected. As such, the dosimetry might be manipulated by falloff dose polarization so that the compactness criteria are met with an "acceptable" deviation of normal tissue constraints.

4.6.2 Specific Strategies

Tumors very near or abutting serially functioning normal structures (e.g., esophagus, great vessels, etc.) make it difficult to meet normal tissue constraints while giving compliant target dose coverage. PTV expansions may cross into adjacent normal tissues confounding the ability to respect the constraint. The planning priorities listed in the previous section must be respected. In cases where a higher priority takes precedence over a normal tissue constraint, attempts should non-the-less be made to spare as much high and intermediate dose to the normal tissue as possible. Specifically, since the prescription dose in each arms is only required to cover 95% of the PTV volume, the 5% not fully covered by the prescription dose can be purposefully manipulate to anatomically occur in the vicinity of a critical normal structure or in the portion of a PTV/normal tissue overlap. While 90% of the prescription dose must still cover the target, this allows the planner to at least lower the maximum dose to the adjacent structure to around 90% of the prescription dose with corresponding lowering of dose fall-off as well. This strategy potentially used for non-spinal cord serial tissues is depicted in the following figure (note: respecting the spinal cord constraints takes precedence over all priorities).



4.7 Critical Structures

4.7.1 Critical Structure Dose-Volume Limits

The following tables list dose limits to a point or volume within several critical organs/tissues for a variety of total fractions. **For the spinal cord, these are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation**. For the non-spinal cord tissues, acceptable deviation allows a maximum point dose no more than 105% of the prescription dose for structures within 1 cm of a PTV target while fully respecting the defined volume constraint (for serial tissues) OR exceeding the parallel tissue critical volume dose maximum by no more than 5%. Unacceptable deviation exceeds the volume constraint for serial tissues, exceeds the maximum point dose for serial tissues by more than 105% of the prescription dose, or exceeds the parallel tissue critical volume dose maximum by more than 5%.

The normal tissue constraints listed in the following table list **total dose** for a specified total number of fractions. Participating centers are encouraged to observe prudent treatment planning principles in avoiding unnecessary radiation exposure to critical normal structures irrespective of these limits.

Three Fractions

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)**	Endpoint (≥Grade 3)
Spinal Cord	<0.35 cc <1.2 cc	15.9 Gy 13 Gy	22.5 Gy	myelitis
Cauda Equina	<5 cc	21.9 Gy	25.5 Gy	neuritis
Sacral Plexus	<5 cc	22.5 Gy	24 Gy	neuropathy
Esophagus*	<5 cc	17.7 Gy	25.2 Gy	stenosis/fistula
Heart/Pericardium	<15 cc	24 Gy	30 Gy	pericarditis

Great vessels	<10 cc	39 Gy	45 Gy	aneurysm
Rib	<5 cc	40 Gy	50 Gy	Pain or fracture
Skin	<10 cc	31 Gy	33 Gy	ulceration
Stomach	<5 cc	22.5 Gy	30 Gy	ulceration/fistula
Bile duct			36 Gy	stenosis
Duodenum*	<5 cc <10 cc	15.6 Gy 12.9 Gy	22.2 Gy	ulceration
Jejunum/Ileum*	<30 cc	17.4 Gy	27 Gy	enteritis/obstruction
Colon*	<20 cc	24 Gy	34.5 Gy	colitis/fistula
Ureter			40 Gy	stenosis
Renal hilum/vascular trunk	15 cc	19.5 Gy		malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	1500 cc	10.5 Gy		Basic Lung Function
Lung (Right & Left)	1000 cc	11.4 Gy	V-11Gy<37%	Pneumonitis
Liver	700 cc	17.1 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc	15 Gy		Basic renal function

*Avoid circumferential irradiation
** "point" defined as 0.035cc or less

Four Fractions

Serial Tissue	**Volume**	**Volume Max (Gy)**	**Max Point Dose (Gy)****	**Endpoint (≥Grade 3)**
Spinal Cord	<0.35 cc <1.2 cc	18 Gy 14.6 Gy	25.6 Gy	myelitis
Cauda Equina	<5 cc	26 Gy	28.8 Gy	neuritis
Sacral Plexus	<5 cc	26 Gy	28 Gy	neuropathy
Esophagus*	<5 cc	18.8 Gy	30 Gy	stenosis/fistula
Heart/Pericardium	<15 cc	28 Gy	34 Gy	pericarditis
Great vessels	<10 cc	43 Gy	49 Gy	aneurysm
Rib	<5 cc	43 Gy	54 Gy	Pain or fracture
Skin	<10 cc	33.6 Gy	36 Gy	ulceration
Stomach	<5 cc	25 Gy	33.2 Gy	ulceration/fistula
Bile duct			38.4 Gy	stenosis
Duodenum*	<5 cc <10 cc	17.2 Gy 14 Gy	24.4 Gy	ulceration
Jejunum/Ileum*	<30 cc	18.8 Gy	30 Gy	enteritis/obstruction
Colon*	<20 cc	26 Gy	37.2 Gy	colitis/fistula
Ureter			43 Gy	stenosis
Renal hilum/vascular trunk	15 cc	21.5 Gy		malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	1500 cc	11.6 Gy		Basic Lung Function
Lung (Right & Left)	1000 cc	12.4 Gy	V-13Gy<37%	Pneumonitis
Liver	700 cc	19.2 Gy		Basic Liver Function

Renal cortex (Right & Left)	200 cc	17 Gy		Basic renal function

*Avoid circumferential irradiation
** "point" defined as 0.035cc or less

Five Fractions

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)**	Endpoint (≥Grade 3)
Spinal Cord	<0.35 cc <1.2 cc	22 Gy 15.6 Gy	28 Gy	myelitis
Cauda Equina	<5 cc	30 Gy	31.5 Gy	neuritis
Sacral Plexus	<5 cc	30 Gy	32 Gy	neuropathy
Esophagus*	<5 cc	19.5 Gy	35 Gy	stenosis/fistula
Heart/Pericardium	<15 cc	32 Gy	38 Gy	pericarditis
Great vessels	<10 cc	47 Gy	53 Gy	aneurysm
Rib	<5 cc	45 Gy	57 Gy	Pain or fracture
Skin	<10 cc	36.5 Gy	38.5 Gy	ulceration
Stomach	<5cc	26.5 Gy	35 Gy	ulceration/fistula
Bile duct			41 Gy	stenosis
Duodenum*	<5 cc <10 cc	18.5 Gy 14.5 Gy	26 Gy	ulceration
Jejunum/Ileum*	<30 cc	20 Gy	32 Gy	enteritis/obstruction
Colon*	<20 cc	28.5 Gy	40 Gy	colitis/fistula
Ureter			45 Gy	stenosis
Renal hilum/vascular trunk	15 cc	23 Gy		malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	1500 cc	12.5 Gy		Basic Lung Function
Lung (Right & Left)	1000 cc	13.5 Gy	V-13.5Gy<37%	Pneumonitis
Liver	700 cc	21 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc	18 Gy		Basic renal function

*Avoid circumferential irradiation
** "point" defined as 0.035cc or less

4.7.2 Contouring of Critical Structures

Critical structure contours will be drawn in axial planes of the primary planning dataset. In general, critical structures should be contoured if they are found within an axial slice within 10 cm in the craniocaudal direction of any PTV slice treated on protocol. As such, they may be further than 10 cm direct separation and still required to be contoured. If a named critical structure is further than 10 cm from any PTV, then it need not be contoured or submitted.

Spinal Cord

The spinal cord will be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at least 10 cm above the superior extent of any PTV and continuing on every CT slice to at least 10 below the inferior extent of any PTV. **NOTE: For the spinal cord, constraints are absolute limits, and treatment delivery that exceeds defined limits will constitute a major protocol violation.**

Cauda Equina
Starting at the conus (end of spinal cord, typically around L1 or L2) include the entire spinal canal into the sacrum to the filum.

Esophagus
The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at least 10 cm above the superior extent of any PTV and continuing on every CT slice to at least 10 below the inferior extent of any PTV.

Sacral Plexus
Include the nerve roots from L5 to S3 on each side from the neuroforamina to the coalescing of the nerves at the obturator internus muscle.

Heart
The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aorto-pulmonary window) and extend inferiorly to the apex of the heart.

Whole Lung
Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. All inflated and collapsed lung should be contoured; however, gross tumor (GTV) and trachea/ipsilateral bronchus as defined above should not be included in this structure.

PTV + 2 cm
As part of the QA requirements for “low dose spillage” listed above, a maximum dose to any point 2 cm away in any direction is to be determined (D2cm). To facilitate this QA requirement, an artificial structure 2 cm larger in all directions from the PTV is required. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning. If possible this structure should be constructed as a single contour that is 2 cm larger than the PTV.

Skin
The skin will be defined as the outer 0.5 cm of the body surface. As such it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations (e.g., the scalp on the top of the head).

Rib
Ribs within 5 cm of the PTV should be contoured by outlining the bone and marrow. Typically, several portions of adjacent ribs will be contoured as one structure. Adjacent ribs, however, should not be contoured in a contiguous fashion (i.e., do not include the inter-costal space as part of the ribs).

Stomach
The entire stomach and its contents should be contoured as a single structure as a continuation of the esophagus and ending at the first part of the duodenum.

Duodenum
The wall and contents of the 1st, 2nd, and 3rd parts of the duodenum will be contoured as one structure beginning where the stomach ends and finishing as the superior mesenteric artery crosses over the third part of the duodenum.

Jejunum/Ileum
As a conglomerate of bowel loops within the abdomen distinguished from stomach, duodenum,

and colorectum.

Colon
From the ileocecal area to include the ascending, transverse, descending and sigmoid colon as one structure.

Renal Hilum
The collecting system of calyces within the kidney to the pelvis of the kidney and proximal ureters

Renal Cortex (right and left combined as one)
Specifically, the parallel functioning nephrons of the renal cortices of the kidneys (not the hilum).

Liver
The entire liver minus the GTV targets.

Bile ducts
May use the portal vein from its juncture with the splenic vein to it's right and left birfurcation in the liver as a surrogate to identify the bile ducts.

Other Structures
The constraints tables above contain other structures. These are required if the structure is within 10 cm of the PTV.

4.8 SABR Compliance

4.8.1 Dosimetry Compliance

RT treatment plans not meeting the "per protocol" criteria or scored as "variation acceptable" will be classified as "deviation unacceptable." Normal tissue dose constraints are listed above. **NOTE: For the spinal cord, these are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation.** For the non-spinal cord tissues, acceptable deviation following the planning priorities allows a maximum point dose no more than 105% of the prescription dose while fully respecting the defined volume constraint (for serial tissues) OR exceeding the parallel tissue critical volume dose maximum by no more than 5%. Unacceptable deviation exceeds the volume constraint for serial tissues, exceeds the maximum point dose for serial tissues by more than 105% of the prescription dose, or exceeds the parallel tissue critical volume dose maximum by more than 5%.

4.8.2 Contouring Compliance

Accurate and appropriate contouring is essential for the generation of dose volume statistics. In addition, it is the desire of the investigator to compile a comprehensive database of dose volume information coupled with outcomes data (control/toxicity) in order to define accurate dose response effects. As such, we require that the tumor targets and normal tissues in the vicinity be contoured in all patients. In particular, any structure listed with a constraint in Critical Structures and residing within 10 cm in any direction from the PTV must be contoured. Appropriateness of contouring will be scored by the study PIs as either no deviation, minor deviation, or major deviation.

4.9 Toxicities and Dosing Delays/Dose Modifications

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table (See section 5.4). Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0 and RTOG/EORTC acute and late toxicity criteria as described in http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx and in Appendix B and C. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

4.10 Duration of Therapy

No more than three SABR fractions will be delivered per week. Therefore the treatment duration will be between 2-3 weeks depending on the fractionation scheme chosen.

4.11 Duration of Follow Up

Subjects will be followed for 2-5 years with MRI scans every 6 months for the first year and if there is no growth then every six months subsequently; if there is evidence of growth, frequency will be determined by physician.

4.12 Removal of Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator, and document the reason for study removal and the date the subject was removed in the Case Report Form. The subject should be followed-up per protocol.

4.13 Subject Replacement

The following are criteria for subject replacement: 1) If the subjects decide to withdraw from the study without finishing the course of SABR, 2) if the subjects decide to withdraw from the study or lost to follow up (for reasons of death from other causes, moving to other state etc.) or refuse follow up scans leading to <3 follow-up scans or <1 year of follow up, 3) if the subjects become unable to undergo an MRI or contrast enhanced CT scan with <1 year of follow up.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within two months prior to registration unless otherwise stated. The screening procedures include:

5.1.1 *Informed Consent*

5.1.2 *Medical history*

Complete medical and surgical history, history of infections, history of previous cancers, history of previous radiation, family history of cancers.

5.1.3 *Demographics*

Age, gender, race, ethnicity

5.1.4 *Review subject eligibility criteria*

5.1.5 *Review previous and concomitant medications*

5.1.6 *Physical exam including vital signs, height and weight*

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

5.1.7 *Performance status*

Performance status evaluated prior to study entry according to ECOG performance scale.

5.1.8 *Adverse event assessment*

Baseline adverse events will be assessed prior to the beginning of treatment See section 7.0 for Adverse Event monitoring and reporting.

5.1.9 *Hematology*

CBC with differential

5.1.10 *Blood draw for correlative studies*

See Section 8.0 for details.

5.1.11 *Serum chemistries*

Comprehensive metabolic panel (CMP) to include: albumin, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, phosphate and calcium.

5.1.12 *Urine analysis*

Urine analysis including RBC, WBC, protein, creatinine, protein to creatinine ratio.

5.1.13 *Pregnancy test (for females of child bearing potential)*

Standard urine pregnancy test will be used to rule out pregnancy

5.1.14 *Biopsy of Renal lesion*

5.1.14.1 Pre-treatment biopsy:

A CT-guided biopsy of a tumor lesion will be performed prior to study registration, unless previous biopsy of the same lesion is performed within the last one year exists and a review of slides shows it to be adequate, in which case a pretreatment biopsy is optional.

5.1.14.2 Post-treatment biopsy:

A post-treatment biopsy will be performed at one year post treatment regardless of whether clinical indication (tumor growth >4mm, enhancement, etc.) is present or not.

5.1.15 Tumor assessment

Tumor assessment will be performed using MRI with (preferred) or without contrast, or contrast enhanced CT. A growth of >2mm of tumor size within one year period must be demonstrated to meet be eligible for this study.

5.1.16 Kidney function assessment:

Kidney perfusion assed by Renal scinctigraphy scan performed at baseline and at one year post treatment.

5.2 Procedures during Treatment

SABR treatment will be delivered either in three, four or five fractions. For a given lesion (target), a minimum of 40 hours and a maximum of 8 days should separate consecutive treatments. All treatment must be completed within 21 days.

5.2.1 Prior to starting first SABR treatment: Baseline assessment is sufficient and need not be repeated if done within the past two months

- Physical exam, vital signs

5.2.2 Day 1

- First fraction of SABR
- Correlative Blood draw 1-2 hours after first SABR fraction only (see section 8).

5.2.3 4 weeks (+/-1 week) after treatment termination

- Physical Exam: including: medical history and vital signs
- Hematology
- Serum chemistries
- Lab corollary blood draw
- Urine Analysis
- Performance status
- Toxicity evaluation

5.3 Follow-up Procedures

Subject will be followed at every six months (+/- 2 weeks) thereafter for five years after their first follow up at 1 month (+/- 1 week).
With every visit, patients will have:

- Physical exam including: vital signs, weight, height and BMI
- MRI with or without contrast or CT with contrast
- Renal scinctgraphy scan at 1 year
- Hematology
- Serum Chemistries
- Urine Analysis
- Lab corollary blood draw at 1 month and six month
- Performance status
- Toxicity evaluation
- Tumor measurements

*Note: Subjects who show progressive disease or develop a new primary will be followed for survival only and will no longer strictly adhere to study calendar.

5.4 Time and Events Table

	Pre-study Within 2 months prior to registration	Day 1 First SABR	At One month (+/- 1 week)	q6 Months (+/- 2 weeks)	At one year (+/- 2 weeks)
Assessment	X				
Informed Consent	X				
Diagnostic/ Pre-treatment Renal Bx	X				
Post-treatment Renal Bx					X
Physical Exam	X	X	X	X	
Performance Status	X		X	X	
Toxicity Evaluations			X	X	
Tumor Measurements	X			X	

Chemistry	X		X	X	
CBC	X		X	X	
Correlative Labs	X	X*	X*	X*	
Urine Analysis	X		X	X	
MRI or CT	X			X	
Renal Scan	X				X

*Correlative labs will be drawn at baseline, on first day of SABR (see section 8), at one month and at 6 month after SABR.

5.5 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Subject voluntarily withdraws from treatment (follow-up permitted);

5.5.2 Subject withdraws consent (termination of treatment and follow-up);

5.5.3 Subject is unable to comply with protocol requirements;

5.5.4 Subject demonstrates disease progression (follow-up permitted)

5.5.4.1 Tumor size >4cm

5.5.4.2 Loco-regional progression as defined in AJCC 7; stage >T1a.

5.5.5 Subject experiences toxicity that makes continuation with the remaining SABR fractions unsafe;

5.5.6 Treating physician judges continuation on the study would not be in the subject's best interest;

5.5.7 Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event) prior to the completion of SABR treatments;

5.5.8 Subject becomes unable to undergo imaging studies after enrollment, subject will be either replaced or withdrawn from study based on investigator's assessment;

5.5.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires systemic treatment which could interfere with this study;

5.5.9 Lost to follow-up. If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.

6.0 Measurement of Effect

6.1 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

6.1.1 Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with SABR.

Evaluable for objective response. Only those subjects who have measurable or non-measurable disease present at baseline, have received ALL fractions of SABR and have had their disease re-evaluated with a minimum of one year of follow up will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below.

6.1.2 Disease Parameters

Measurable Disease: Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

1. 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
2. 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
3. 20 mm by chest x-ray.

Non-measurable disease.
All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Target lesions.
All measurable lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions.

All measurable lesions should be recorded and measured at baseline. A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

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

6.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment planning session.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT with contrast: These techniques should be performed with cuts of 1 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

MRI: Will be performed with gadolinium if possible. These techniques should be performed with cuts of 1 mm or less in slice thickness contiguously.

6.1.4 Response Criteria

6.1.4.1 Evaluation of Lesions

Complete Response (CR): Disappearance of all target lesions. Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes). Determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): > 20% increase in the SLD taking as reference the smallest SLD recorded since the treatment started (nadir) and minimum 5 mm increase over the nadir.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started. There can be no unequivocal new lesions.

Tumor Growth (TG): At least a 4mm increase in the LD of treated lesion in a single scan when compared to baseline scan (or an increase of >2.0mm in two consecutive scans).

Local Control: No TG AND a complete radiographic or pathologic absence of tumor viability.

Local Failure: Any TG OR any radiographic or pathologic evidence of tumor viability.

Indeterminate Disease Response: (IDR): 1) Presence of radiographic evidence of viable disease without any increase in the LD (<4mm) sufficient enough to qualify for TG; 2) complete absence of radiographic evidence of viable disease regardless of any change in tumor diameter.

A biopsy is recommended in the case of tumors with ≥4mm increase in size with no radiographic evidence of viable tumor, OR any tumors with radiographic evidence of viable tissue.

6.1.4.2 Evaluation of Non-Target Lesions

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

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

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

6.1.4.3 Evaluation of Best Overall Response

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

Time point response: patients with target (+/– non-target) disease.			
Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, NE = not evaluable, PD = progressive disease, PR = partial response, SD = stable disease.

Time point response: patients with non-target disease only.		
Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, NE = not evaluable, PD = progressive disease

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

6.1.5 Duration of Response

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

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

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

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

6.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

6.2 Pathologic Response:

The pathologic response is evaluated by a required 1-year post-treatment biopsy where the tumor viability must be confirmed on FFPE tissue with appropriate staining (Ki67, PHH3, mitotic index etc.) showing continued tumor proliferation as compared to pre-treatment biopsy tissue.

6.3 Safety/tolerability

Analyses will be performed for all subjects having received at least one fraction of radiation of study intervention. The study will use the CTCAE version 4.0 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html) and modified criteria for hematologic adverse events (Appendix #/letter).

7.0 ADVERSE EVENTS

7.1 SABR

The contraindications and adverse events for SABR are mostly related to the location of the SRM in relation to renal pelvis and its distance from loops of small bowel which is the most radio-sensitive organ nearby. The allowed radiation dose constraints of the kidney, small bowel and all the other nearby organs are discussed in detail in section 4.1

7.1.1 Contraindications: None

7.1.2 Special Warnings and Precautions for Use: N/A

7.1.3 Interaction with other medications: None

7.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study intervention, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse

event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study intervention for the changes observed; or
- death.

7.2.1 Definition

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected. **Acute Adverse Events**

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research. Adverse events occurring through the time period of the start of treatment through the first follow up occurring 12 weeks post treatment will be considered acute adverse events. All acute adverse events will be assessed and reported as per below.

Late Adverse Events

Adverse effects occurring in the time period from the end of acute monitoring, to 3 years post treatment for progression or death (whichever comes first), will be defined as late adverse events. These events will include all adverse events reported directly to a member of the study team and will be captured, assessed, graded and reported as appropriate.
In addition, the study team will review encounters in a select specialty category relevant to study endpoints. These select specialties include hospitalizations, medical oncology, and radiation oncology records and will be limited in scope based on categorization of events (GU/GI) and also the type of records that will be queried (hospitalizations, medical oncology, and radiation oncology).

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Severity

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE v4 is available at http://ctep.cancer.gov/reporting/ctc.html

Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets any of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring >24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

1Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

7.2.2 2 NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report. Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The phrase "unanticipated problems involving risks to subjects or others" is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR

56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

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;

AND

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 greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

7.3 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy.
Attribution categories are as follows:

- 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 *may NOT be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure
- the radiation therapy known toxicities section of this protocol

7.3.1 Reporting SAEs and UPIRSOs to the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC)

All SAE/UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs/UPIRSOs occurring during the protocol-specified monitoring period should be submitted to the SCCC DSMC within 5 business days of the PI or delegated study team members awareness of the event(s). In addition, for participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events.

The UTSW study team is responsible for submitting SAEs/UPIRSOs to the SCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE/UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if further action is required. *(See Appendix III of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB is not required).*

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Comprehensive Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all SAEs/UPIRSOs upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

The following instructions section may be modified as needed to ensure clear guidance for institutions participating in the trial who will not report directly to the UTSW Institutional Review Board. If needed, this reporting may be facilitated by the UTSW study team for example.

Telephone reports to: (Investigator/study team: Insert names and phone numbers for required notifications)
Written reports to: (Investigator/study team: Insert names, fax numbers, an addresses for required notifications) UTSW SCCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-5949 or deliver to BLB.306 UTSW Institutional Review Board (IRB) Submit a Reportable Event via eIRB with a copy of the final sponsor report as attached supporting documentation

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP/IRB

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP/IRB policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. 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. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

For purposes of this policy, UPIRSOs include unanticipated adverse device effects (UADEs) and death or serious injury related to a humanitarian use device (HUD).

UPIRSOs must be promptly reported to the UTSW IRB within 5 working days of PI awareness.

For research relying on a non-UT Southwestern IRB (external, central, or single IRB):

Investigators relying on an external IRB who are conducting research on behalf of UT Southwestern or its affiliates are responsible for submitting **LOCAL** UPIRSOs to the UT Southwestern IRB within 5 working days of PI awareness. Investigators must report to their relying IRB according to the relying IRB's policy. In addition, the external IRB's responses or determinations on these local events must be submitted to the UT Southwestern IRB within 10 working days of receipt.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/research-administration/irb/assets/policies-combined.pdf.

7.4 Stopping Rules

Interim analysis will be performed after enrollment of 6 patients. The stopping rules for study includes grade 3 acute toxicity in >30% of enrolled patients, and tumor progression/growth in >50% of enrolled patients.

8.0 CORRELATIVES/SPECIAL STUDIES

The goal of the planned laboratory correlative studies is to measure the induced immune response to patient's pre-treatment tumor tissue antigens (see section 1.5 for detail). In addition,

the correlative studies will evaluate the immune response generated by the regiment. The submission of collected whole blood before, during and post treatment as indicated in Section 5 is mandatory and will be performed at baseline, during RT (1-2 hours after first SABR fraction), at 4 weeks and at 24 weeks. A CT-guided biopsy of a tumor lesion will be performed prior to study registration, unless previous biopsy of the primary lesion is performed within the last one year exists and a review of slides shows it to be adequate, in which case a pretreatment biopsy is optional. The one year post-treatment biopsy will be processed the same way as the pre-treatment biopsy.

8.1 Sample Collection Guidelines

Samples will be labeled with the subject's de-identified study number and collection date and delivered for analysis during regular business hours to: NC7: 208; Attn Dr. Raquibul Hannan.

8.1.1 Whole blood sample: Patient's whole blood will be collected in EDTA (Lavender top) tubes for ~ 100 ml at baseline, at 4 weeks (+/- 1 week) and at six months starting from the first day of study registration for immunologic assays. In addition, 10 ml will be collected in anti-coagulant-free tubes (Red top) for the collection of sera. The only exception is the blood collection one hour post first SABR fraction which will be for 20ml in EDTA and 20 ml in anti-coagulant-free tubes. The blood will immediately be processed (within 2 hours) by centrifugation (1000g, 15min, 4 ^{o}C), collecting the supernatant and freezing at -80 ^{o}C in 5 aliquots for future experiments. The pellet will be re-suspended in PBS and PBMC will be isolated using standard protocol. Briefly, the cell suspension will be carefully placed on 10ml polystyrene tube containing 1ml ficoll and centrifuged (400g, 30min, RT). Collect the PBMC region from the ficoll and washed 3x with PBS. Count and freeze cells in 5 aliquots with 10%DMSO 90%FBS in -80^{o}C.

8.1.2 Renal mass biopsy sample: An image-guided biopsy of tumor lesion consisting of 4-5 18G needle cores is recommended at the time of registration of the patients to the study. A second biopsy at one year after the SABR treatments is required.

8.1.2.1 Initial required biopsy: 3-4 core biopsies will be processed as routine diagnostic specimens by Pathology for the purpose of diagnosis and Immumo-histochemistry (IHC). After on site adequacy check using touch imprint slides, the cores will be fixed in 10% buffered formalin for up to 8 hours and processed routinely to obtain formalin fixed paraffin embedded blocks. Eight, 3-micron thick sections will be cut. The first and last sections will be stained with hematoxylin and eosin (H&E) stain to evaluate the presence, extent, and grade of renal carcinoma. The remaining sections will be used to perform immunohistochemical staining if needed. (see section 8.2.6 for IHC detail). **Two additional cores** will be placed in normal saline on wet ice and brought to NC9.208 (Dr. Raquibul Hannan) for generation of tumor lysates to be used as a source of antigen in the immunoassays. The biopsy cores will be chopped into minute pieces. Small volume of normal saline is added and the mixture is passed through a 19G needle, attached to a 5 ml syringe, several times, until the passage of the mixture occurred without difficulty. The process is repeated with 21G, 23G, and if possible 25G needle. The entire mixture is placed in liquid nitrogen until frozen, and then thawed in a water bath at 42°C. The freezing and thawing is repeated for a total of five times. The sample is passed through another 23G or 25G needle to disperse any clumps. The sample is then centrifuged at high speed, the

supernatant collected, protein concentration measured using NanoDrop2000 and frozen at -80 ºC in 5 aliquots.

8.1.2.2 One-year Biopsy: Processed same as initial biopsy.

8.2 Assay Methodology

8.2.1 Elispot: IFN-□ ELISpot assays will be performed according to manufacturer's protocol using a commercial ELISpot kit (MabTECH). Briefly, 96 well plates are coated overnight with 0.015 mg/ml of an anti-human IFN-g monoclonal antibody. PBMC from patients will be incubated in triplicates wells and stimulated in the presence of either protein lysate from patient biopsy (50µg/ml) or 5 ng/ml PMA and 0.5 ng/ml ionomycin as positive control and albumin as negative control. For ELISPOT assays, plates are incubated for 48 hours, washed, probed with biotinylated anti-IFNg, further washed, and then incubated with streptavidin alkaline phosphatase. Spot development is achieved with 5-bromo-4-chloro-3-indolyl phosphate/nitroblue tetrazolium (BCIP/NBT; Invitrogen) and spots are enumerated by an automatic ELISpot reader.

8.2.2 ELISA: In this procedure, patient tumor tissue lysate is first adsorbed to an EIA 96 well microplate (Fischer). Patient plasma is then added to each well as a source of primary antibody and serially diluted. After extensive washes, detection enzyme (HRP)-linked anti-human mAb is then added to each well and allowed to bind. Appropriate substrate is then added to each well and color development occurs within 5-60 min. UV Microplate Reader will be used to read the plates

8.2.3 ^{3}H-thymidine Proliferation Assay: PBMC from patients will be incubated in a similar manner as above for five days at 37 ºC then overnight with 0.5 mCi tritiated ^{3}H-thymidine, harvested onto a glass-fiber filter using a 96-well FilterMate cell harvester. The radioactivity of the ^{3}H-thymidine is detected by a direct betaplate counter. The degree of antigen-specific clonal T cell expansion will be expressed as a stimulation index (SI) of the ratio of ^{3}H-thymidine incorporation by cells incubated with patient tumor lysate compared with media controls. An alternate method utilizing FACS analysis with carboxy fluorescein diacetate succinimidyl ester (CFSE) is also available [95].

8.2.4 Chromium Release Cytotoxicity Assays: For cell-mediated cytotoxicity analysis, A 50 µl sample of ^{51}Cr-labeled target cells (Caki-2 and ACHIN human renal cancer cells) is mixed with 100µl of effector cells (patient PBMC) at various target to effector ratio (E:T ratios). After centrifugation at 100 X G, the cells are incubated for 2 hr at 37°C. The radioactivity of culture supernatant is measured using a gamma counter and percentage of cytotoxicity is calculated. For antibody-dependent cytotoxicity analysis this procedure will be performed with patient's plasma instead of PBMC and the percentage of cytotoxicity is calculated in similar manner. An alternate and non-radioactive labeling method utilizes GAPDH enzyme release from lysed cells called Bioluminescence Non Radioactive Cytotoxicity Assay (aCella-TOX, T Cell Technology, INC) [96, 97].

8.2.5 Flow cytometric analysis (FACS): For FACS analysis of cell-surface molecules, the cell samples are stained with fluorescent dye – conjugated monoclonal antibodies against the selected markers on ice followed by fixation with 4% paraformaldahyde. Data are acquired on a LSRII (BD Biosciences) and analyzed using FACSDiva software (BD Biosciences). The PBMC of each patient before and after treatment will be analyzed to identify the relative sub-population of CTLs,

regulatory T-Cells, effector memory T cells, MDSCs, neutrophils and NK cells utilizing appropriate cell surface markers (see section 1.5).

8.2.6 Immunohistochemical staining (IHC): Standard immunohistochemistry staining procedure will be performed using the Benchmark XT automated stainer (Ventana) for both antibodies. Briefly, formalin-fixed, paraffin-embedded tissue sections will be cut at 3-4 micron and air-dried overnight. The sections will be deparaffinized, rehydrated, and subjected to heat-induced epitope retrieval. Sections will then be incubated with appropriate primary antibody. For signal detection, ultraView universal detection system (Ventana) will be used. The slides will be developed using 3-3'-diaminobenzidine chromogen and counterstained with hematoxylin. Appropriate positive and negative controls will be utilized for each run of immunostains. The evaluation of the immunostaining will be carried out by a genitourinary pathologist without knowledge of any clinicopathologic data. Only nuclear reactivity will be considered positive. An H score will be assigned as the product of average intensity of staining (0 for negative, 1 for weakly positive, 2 for moderately positive, and 3 for strongly positive) and extent of immunoexpression (0-100% percentage of cells staining). In addition, Dual-antibody ISH will be performed to identify and analyze TILs, CTL (CD3+,CD8+), Tregs (CD4+FoxP3), DC (CD11c) , NK/T (CD3+, CD1d), neutrophils (CD11b, Ly6G} and MDSC (CD14+,CD11b) in the tumor tissue before and after treatment, when available (see section 1.5).

8.2.7 Serum Cytokine Analysis: Multiplex cytokine analysis in patient's plasma will be performed in precoated 96 well plates (Human TH1/TH2 10 plex ultrasensitive assay, Meso Scale Discovery – MSD, Maryland, USA) according to manufacturer's instructions. 25 µL of diluent 2 is dispersed into each well. The plate is sealed and incubated by vigorous horizontal shaking for 30 minutes at RT. 25 µL of the patient plasma is added per well and all samples measured in triplicates. Plates are sealed and incubated by vigorous horizontal shaking for two hours at RT. Plates are washed three times with 0.05% Tween 20 in PBS . 25 µL of 1× detection antibody solution is placed per well and sealed plates are incubated by vigorous horizontal shaking for two hours at RT. Plates are washed three times with 0.05% Tween 20 in PBS. 150 µL of 2× Read Buffer T is added to each well. Plates are analysed using the MSD SECTOR Imager 2400 and Discovery Workbench 3.0 software (both from Meso Scale Discovery, USA). The mean value of two wells is taken as the recorded reading, provided that the coefficient of variation (CV) was less than 10%. Concentrations recorded lower than the standard curve are kept as absolute values. For purposes of logarithmic analysis, readings of 0 are adjusted to 0.01 pg/ml. The following cytokines will be measured before and after treatment for each patients: Th1/Th2/Th17 cytokines, IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12p70, IL-13, IL-17 TNF-α; pro-inflammatory cytokines: GM-CSF, IFN-γ, IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12p70, TNF-α; Chemokines: Eotaxin, MIP-1β, TARC, IP-10, IL-8, MCP-1, MCP-4 and others including IL-6, TGF-β and HMGB1 (see section 1.5).

8.2.8 Western-blot/Immuno-blot: Caki-2 and ACHIN human renal cancer cells lysate will be used to perform immune-blott using plasma collected from patients before and after treatment. The Caki-2 and ACHIN cell 10^6 cells/mL will be lysed in immunoprecipitation assay buffer on ice for 30 min. Standard western blott methodology will be utilized. Briefly, 400 µg of protein will be separated using pre-made gradient 4% to 12% Bis-Tris gels (Invitrogen, Burlington, ON, Canada) and transferred to nitrocellulose. Patient sera/plasma will be diluted 1/500 in Blotto (5% dry milk powder; 0.1% Tween 20; 50 mmol/L Tris; 150 mmol/L NaCl) and incubated with nitrocellulose membranes for 1 h at room temperature using a multichannel immuoblotting device (Mini Protean II Multiscreen, Bio-Rad,

Missassauga, ON, Canada). The membrane will then incubated for 1 h at room temperature with horseradish peroxidase–conjugated goat anti-human IgG (H+L; Jackson ImmunoResearch, West Grove, PA) diluted 1/10,000 in Blotto and visualized by enhanced chemiluminescence**.**

8.2.9 Gene expression analyses: The current Illumina whole genome DASL platform allows for the interrogation of over 29,000 genes based upon the RefSeq (Build 36.2, release 38) database. This assay requires 50-200 ng of total RNA from archival FFPE samples or 10-100 ng total RNA from fresh frozen tissue. RNA will be isolated using the one column protocol from the Roche High Pure miRNA Paraffin Kit, which isolates total RNA, including miRNA. A 3mm x 10um section is sufficient to generate 200 ng total RNA from archival specimens. A cDNA pool is created using oligodT and random primers. The cDNA pool is interrogated using a paired 5' and 3' gene-specific 50-mer probes (annealing and selection) that also contain universal primer sequence. Probe extensions are ligated and then PCR amplified using the universal primer pairs. The PCR product is captured using standard Illumina bead technology and hybridized to the Illumina HT12 V4 chip and scanned. Expression values are highly reproducible ($r^2 > 0.97$) and are similar to results by qPCR ($r^2 > 0.85$). mRNA expression of specific genes by qRT-PCR will serve to validate DASL results as needed.Caki-2

8.3 BOLD/TOLD MRI

The BOLD/TOLD MRI sequences will be added to the routine MRI sequences (T1, T2 etc.) performed at baseline and at follow-up, which may require additional time on the MRI table (~30minues), but will not require any additional infusions or intravenous contrast as described in literature previously [98, 99]. These additional sequences will be optional.

8.4 Tumor respiratory motion modeling

Real-time optical surface monitoring data will be acquired from human patients with primary or metastatic kidney lesions during and after their 4DCT scan (standard-of-care at our institution). A patient-specific 4D model will be developed using the raw 4DCT projections time-correlated with real-time surface monitoring. In addition, before delivering each dose fraction, we will acquire three 15s kV fluoroscopic image acquisitions, time-correlated with optical surface monitoring. The acquisitions will be distributed over three well-spaced beam angles, e.g., every 4^{th} angle for a 12-field plan.

The kV fluoro data will be used offline to update and validate the model as follows. The data acquired from the three beam angles will be used in a "missing-view" fashion, i.e., two of the three fluoro sequences will be used to update the model and the third will be used to validate the model. The ground truth will be the in-plane X-Y trajectories of features-of-interest obtained from kV fluoro. The model will be used to create 2D+t digitally reconstructed fluoroscopic series (DRFs) from the beam's eye view of each kV beam. The model will be validated by calculating the geometric error between the trajectories from the kV fluoro (ground truth) and those obtained from the corresponding DRFs.

Surface monitoring procedure —The procedure is expected to last approximately 15 minutes after the end of the 4DCT scan, which is the standard-of-care at our institution. The procedure will consist of real-time surface tracking using the VisionRT system of the thoracic and/or abdominal region. Continuous audiovisual contact will be maintained with the subject during scanning. Each individual will be informed that they can stop the procedure at any point.

Fluoroscopic imaging procedure – Fluoroscopic imaging will be performed in the treatment room with the patient lying in treatment position. Three 15s acquisitions will be performed under free breathing conditions, each from a different beam angle, using the on-board kV imager. Audiovisual contact will be maintained at all times with the patient.

All surface monitoring will be performed using a surface photogrammetry system (VisionRT, London, UK) which uses visible light to monitor the motion of the surface. There are no known significant risks with this procedure at this time. This device and procedure is low-risk.

For the fluoroscopic acquisition, we estimate that for three 15 s acquisitions, each at 10 frames/s, 120 kVp, 40 mA, 10 ms, with 0.1 mGy/mAs, the total skin dose will be ~24 mGy – comparable to that from a kV cone-beam CT (CBCT) scan [100, 101]. Daily CBCT is standard-of-care for patient localization for SBRT at UT Southwestern. No additional ionizing radiation, other than the kV fluoro and standard-of-care, will be administered to the patient as a result of this aspect of the study.

8.5 Specimen Banking

Subject samples collected for this study will be retained at the department of pathology and at the lab of Dr. Hannan (NC7. 208). Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the subject, best efforts will be made to stop any additional studies and to destroy the specimens.

Raquibul Hannan will be responsible for reviewing and approving requests for clinical specimen from potential research collaborators outside of UTSW. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimen will be the property of UTSW for publication and any licensing agreement will be strictly adhered to.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by UTSW, the investigator or a collaborating researcher or entity.

The following information obtained from the subject's medical record may be provided, among other, to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Study Endpoints

This is an open label single-arm phase II non-randomized prospective single arm study that treats a single SRM with SABR. The primary objective is local control of the SRMs. Local control is defined as less than 4mm increase in the longest diameter of tumor measured using either MRI or contrast enhanced CT scan and with no radiographic or pathologic evidence of viable tumor. The endpoint will be measured at a minimum follow up of one year. Secondary objections and endpoints explore the safety, toxicity, growth, growth rate, local failure, IDR, immune response and progression of the SRMs after SABR.

The stopping rules for this study include any treatment-related >grade 3 toxicity. If there are any treatment related grade 3 acute toxicity in >30% of enrolled patients after enrollment of at least 6 patients, the study will be suspended until permitted by a safety review.

9.2 Sample Size and Accrual

There is no reliable historic information on local control rate of SABR for primary RCC since the retrospective studies have used a wide range of SABR dose fractions and varying definitions of local failure. From the retrospective studies and one phase I trial, we found three local failures out of 34 patients (section 1.3). Thus, it is expected that the local control rate will be at least 90% in this trial. With a sample size of 16 patients, the standard error of local control rate will be at most 7.5% with a 95% confidence interval of 15%, since the local control rate is expected to be at least 90%.

A sample size of 16 patients in this single-arm phase II trial will have more than 90% power to detect the difference between 100% pre-treatment tumor growth and 50% post-treatment tumor growth using a two-sided binomial test with a 0.05 significance level. With the sample size of 16 patients in this single-arm phase II trial, a single group t-test with a two-sided 0.10 significance level will have 80% power to detect the difference between a pre-treatment tumor growth rate of 0.4 cm/year and a post-treatment tumor growth rate of 0.16 cm/year (a 60% reduction), assuming that the standard deviation is 0.36 cm/year. The power calculations were conducted using the software PASS 12.

9.3 Data Analyses Plans

The local control rate and the proportion of patients whose tumors did not grow will be estimated along with the corresponding 95% confidence interval using the exact binomial method. The frequency of the adverse events associated with the administration of SABR to SRMs will be computed. Descriptive statistics such as mean, range, and 95% confidence interval will be computed for the growth rate of SRMs after SABR treatment, and the changes in kidney function, creatinine levels, renal perfusion and GFR after SABR treatment. Descriptive statistics will be also computed for radiographic changes of the SRM after SABR treatment, including tumor viability, %enhancement, necrosis, T2 signal, and tumor cellularity with diffusion-weighted imaging.

Kaplan-Meier method will be used to estimate the time to progression (TTP) of disease from the first SABR treatment, progression free survival (PFS), and overall survival (OS). Exploratory data analysis will be conducted to assess the cytokine changes brought on by SABR to SRM and to evaluate generation of any immune response specific to tumor cells.

We will compute the following characteristics of CT and MRI acquired prior to the treatment and follow-up scan: intensity features such as minimum, maximum, mean, standard deviation, median, skewness, kurtosis; texture features such as energy, entropy, correlation, inertia, cluster shade; geometry features such as volume, major axis length, minor axis length, eccentricity, elongation, roundness. The ability of each feature to predict treatment response will be quantified by the area under the receiver operating characteristic curve (AUC). An AUC of<0.7 will be considered to have low accuracy, 0.7-0.9 to have moderate accuracy, and >0.9 to have high accuracy.

10.0 STUDY MANAGEMENT

10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

10.3 Required Documentation (for multi-site studies)

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Research Office, Department of Radiation Oncology, UTSW.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list or Federal wide Assurance letter
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if institution} holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

10.4 Registration Procedures

All subjects must be registered with the Clinical Research Office, Department of Radiation Oncology, UTSW, before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Clinical research office Study Coordinator.

10.5 Data Management and Monitoring/Auditing

The monitoring activities are designed to provide safety monitoring, data quality assurance, and oversight of protocols for study progress. The Radiation Oncology Clinical Research Office (CRO) reports serious adverse events (SAEs) to Radiation Oncology Safety Assurance Committee (ROSAC) monthly. These SAEs are also reported to the University of Texas Southwestern Medical Center (UTSW) IRB and

Simmons Comprehensive Cancer Center DSMC. SCCC-DSMC will audit in accordance with the DSMC plan guidelines.

The purpose of the Radiation Oncology Safety Assurance Committee (ROSAC) is to ensure that clinical trial data is accurate and valid and to ensure the safety of trial participants. The plan complies with the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Plan and the University of Texas Southwestern Medical Center (UTSW) IRB guidelines.

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements, as appropriate for the project

ROSAC is charged with developing, implementing, and maintaining the Data and Safety Monitoring Plan. The membership consists of a Medical Director of Clinical Research as well as representation from the following groups: clinical research, nursing, regulatory, pharmacy, physicists, radiation therapists, and faculty. Additional members are contacted to participate as needed.

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT and/or the CRO Multi-Center IIT Monitor. This review includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

For further information, refer to the UTSW SCCC IIT Management Manual.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

Clinical trials are assessed for safety on a continual basis throughout the life of the trial. All SAE's and any AEs that are unexpected and definitely or probably related to study participation are reported to UTSW IRB through an electronic research system per UTSW IRB guidelines. SAEs are reported to the sponsor per specific sponsor requirements. These SAEs are reported to the SCCC DSMC on a real time basis. All local SAEs will be

reported to the SCCC DSMC. SAE reports can be either scanned/emailed to the coordinator of SCCC DSMC or sent through interoffice mail.

10.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.6.1 Exceptions (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:

- intentional on part of the investigator; or
- in the investigator's control; or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)

 Reporting requirement: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation.

10.6.2 Emergency Deviations: include any departure from IRB-approved research that is necessary to:

- avoid immediate apparent harm, or
- protect the life or physical well-being of subjects or others

 Reporting requirement: Emergency deviations must be promptly reported to the IRB within 5 working days of occurrence.

10.6.3 Major Deviations (also called **violations**): include any departure from IRB-approved research that:

- Harmed or placed subject(s) or others at risk of harm (i.e., did or has the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

 Reporting requirement: Major deviations must be promptly reported to the IRB within 5 working days of PI awareness.

10.6.4 Minor Deviations: include any departure from IRB-approved research that:

- Did not harm or place subject(s) or others at risk of harm (i.e., did not or did not have the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Did not affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

 Reporting requirement: Minor deviations should be tracked and summarized in the progress report at the next IRB continuing review.

10.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly

recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

10.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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12.0 APPENDICES

12.1 Appendix A: ECOG Performance Scale

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
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12.2 Appendix B: RTOG Acute Toxicity Scale:

As defined in RTOG website:
http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx

Acute Radiation Morbidity Scoring Criteria

	[0]	[1]	[2]	[3]	[4]
SKIN	No change over baseline	Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating	Tender or bright erythema, patchy moist desquamation/ moderate edema	Confluent, moist desquamatiom other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
MUCOUS MEMBRANE	No change over baseline	Injection/ may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinitis discharge/ may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/ may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
EYE	No change	Mild conjunctivitis with or without scleral injection/ increased tearing	Moderate conjunctivitis with or without keratitis requiring steroids &/or antibiotics/ dry eye requiring artificial tears/ iritis with photophobia	Severe keratitis with corneal ulceration/ objective decrease in visual acuity or in visual fields/ acute glaucoma/ panopthalmitis	Loss of vision (unilateral or bilateral)
EAR	No change over baseline	Mild external otitis with erythema, pruritis, secondary to dry desquamation not requiring medication. Audiogram unchanged from baseline	Moderate external otitis requiring topical medication/ serious otitis medius/ hypoacusis on testing only	Severe external otitis with dischange or moist desquamation/ symptomatic hypoacusis/tinnitus, not drug related	Deafness
SALIVARY GLAND	No change over baseline	Mild mouth dryness/ slightly thickened saliva/ may have slightly altered taste such as metallic taste/ these changes not reflected in alteration in baseline feeding behavior, such as	Moderate to complete dryness/ thick, sticky saliva/ markedly altered taste	-------	Acute salivary gland necrosis

		increased use of liquids with meals			
PHARYNX & ESOPHAGUS	No change over baseline	Mild dysphagia or odynophagia/ may require topical anesthetic or non-narcotic analgesics/ may require soft diet	Moderate dysphagia or odynophagia/ may require narcotic analgesics/ may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss(>15% from pre-treatment baseline) requiring N-G feeding tube, I.V. fluids or hyperalimentation	Complete obstruction, ulceration, perforation, fistula
LARYNX	No change over baseline	Mild or intermittent hoarseness/cough not requiring antitussive/ erythema of mucosa	Persistent hoarseness but able to vocalize/ referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic/ cough requiring antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic/ confluent fibrinous exudate, marked arytenoid edema	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary
UPPER G.I.	No change	Anorexia with <=5% weight loss from pretreatment baseline/ nausea not requiring antiemetics/ abdominal discomfort not requiring parasympatholytic drugs or analgesics	Anorexia with <=15% weight loss from pretreatment baseline/nausea &/ or vomiting requiring antiemetics/ abdominal pain requiring analgesics	Anorexia with >15% weight loss from pretreatment baseline or requiring N-G tube or parenteral support. Nausea &/or vomiting requiring tube or parenteral support/abdominal pain, severe despite medication/hematemesis or melena/ abdominal distention (flat plate radiograph demonstrates distended bowel loops	Ileus, subacute or acute obstruction, perforation, GI bleeding requiring transfusion/abdominal pain requiring tube decompression or bowel diversion
LOWER G.I. INCLUDING PELVIS	No change	Increased frequency or change in quality of bowel habits not requiring medication/ rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs (e.g., Lomotil)/ mucous discharge not necessitating sanitary pads/ rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support/ severe mucous or blood discharge necessitating sanitary pags/abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
LUNG	No change	Mild symptoms of dry cough or dyspnea on exertion	Persistent cough requiring narcotic, antitussive agents/ dyspnea	Severe cough unresponsive to narcotic antitussive agent or dyspnea at rest/ clinical or radiologic evidence of	Severe respiratory insufficiency/ continuous oxygen or assisted ventilation

			with minimal effort but not at rest	acute pneumonitis/ intermittent oxygen or steroids may be required	
GENITOURINARY	No change	Frequency of urination or nocturia twice pretreatment habit/ dysuria, urgency not requiring medication	Frequency of urination or nocturia which is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium)	Frequency with urgency and nocturia hourly or more frequently/ dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with/ without clot passage	Hematuria requiring transfusion/ acute bladder obstruction not secondary to clot passage, ulceration or necrosis
HEART	No change over baseline	Asymptomatic but objective evidence of EKG changes or pericardial abnormalities without evidence of other heart disease	Symptomatic with EKG changes and radiologic findings of congestive heart failure or pericardial disease/ no specific treatment required	Congestive heart failure, angina pectoris, pericardial disease responding to therapy	Congestive heart failure, angina pectoris, pericardial disease, arrhythmias not responsive to non-surgical measures
CNS	No change	Fully functional status (i.e., able to work) with minor neurologic findings, no medication needed	Neurologic findings present sufficient to require home case/ nursing assistance may be required/ medications including steroids/anti-seizure agents may be required	Neurologic findings requiring hospitalization for initial management	Serious neurologic impairment which includes paralysis, coma or seizures>3 per week despite medication/hospitalization required
HEMATOLOGIC WBC (X 1000)	>=4.0	3.0 - <4.0	2.0 - <3.0	1.0 - <2.0	<1.0
PLATELETS (X 1000)	>=100	75 - <100	50 - <75	25 - <50	<25 or spontaneous bleeding
NEUTROPHILS	>=1.9	1.5 - <1.9	1.0 - <1.5	0.5 - <1.0	<0.5 or sepsis
HEMOGLOBIN (GM %)	>11	11-9.5	<9.5 - 7.5	<7.5 - 5.0	-------
HEMATOCRIT (%)	>=32	28 - <32	<28	Packed cell transfusion required	-------

GUIDELINES: The acute morbidity criteria are used to score/grade toxicity from radiation therapy. The critera are relevant from day 1, the commencement of therapy, through day 90. Therafter, the EORTC/RTOG Criteria of Late Effects are to be utilized.

The evaluator must attempt to discriminate between disease- and treatment-related signs and symptoms.

An accurate baseline evaluation prior to commencement of therapy is necessary.

All toxicities Grade 3, 4 or 5* must be verified by the Principal Investigator.

*ANY TOXICITY WHICH CAUSED DEATH IS GRADED 5.

12.3 Appendix C: RTOG/EORTC Late Radiation Morbidity Scoring Schema

As defined in RTOG website:
http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx

RTOG/EORTC Late Radiation Morbidity Scoring Schema

ORGAN TISSUE	0	Grade 1	Grade 2	Grade 3	Grade 4	5
SKIN	None	Slight atrophy Pigmentation change Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration	DEATH DIRECTLY RELATED TO RADIATION LATE EFFE
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosia) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic Slight field contracture <10% linear reduction	Severe induration and loss of subcutaneous tissue Field contracture >10% linear measurement	Necrosis	
MUCOUS MEMBRANE	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia Little mucous	Marked atrophy with complete dryness Severe telangiectasia	Ulceration	
SALIVARY GLANDS	None	Slight dryness of mouth Good response on stimulation	Moderate dryness of mouth Poor response on stimulation	Complete dryness of mouth No response on stimulation	Fibrosis	
SPINAL CORD	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadraplegia	
BRAIN	None	Mild headache Slight lethargy	Moderate headache Great lethargy	Severe headaches Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis Coma	
EYE	None	Asymptomatic cataract Minor corneal ulceration or keratitis	Symptomatic cataract Moderate corneal ulceration Minor retinopathy or glaucoma	Severe keratitis Severe retinopathy or detachment Severe glaucoma	Panopthalmitis/ Blindness	
LARYNX	None	Hoarseness Slight arytenoid edema	Moderate arytenoid edema Chondritis	Severe edema Severe chondritis	Necrosis	
LUNG	None	Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis Dense radiographic changes	Severe respiratory insufficiency/ Continuous O_2/ Assisted ventilation	

HEART	None	Asymptomatic or mild symptoms Transient T wave inversion & ST changes Sinus tachycardia >110 (at rest)	Moderate angina on effort Mild pericarditis Normal heart size Persistent abnormal T wave and ST changes Low ORS	Severe angina Pericardial effusion Constrictive pericarditis Moderate heart failure Cardiac enlargement EKG abnormalities	Tamponade/ Severe heart failure/ Severe constrictive pericarditis	C T S
ESOPHAGUS	None	Mild fibrosis Slight difficulty in swallowing solids No pain on swallowing	Unable to take solid food normally Swallowing semi-solid food Dilatation may be indicated	Severe fibrosis Able to swallow only liquids May have pain on swallowing Dilation required	Necrosis/ Perforation Fistula	
SMALL/LARGE INTESTINE	None	Mild diarrhea Mild cramping Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic Bowel movement >5 times daily Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/ Perforation Fistula	
LIVER	None	Mild lassitude Nausea, dyspepsia Slightly abnormal liver function	Moderate symptoms Some abnormal liver function tests Serum albumin normal	Disabling hepatitic insufficiency Liver function tests grossly abnormal Low albumin Edema or ascites	Necrosis/ Hepatic coma or encephalopathy	
KIDNEY	None	Transient albuminuria No hypertension Mild impairment of renal function Urea 25-35 mg% Creatinine 1.5-2.0 mg% Creatinine clearance >75%	Persistent moderate albuminuria (2+) Mild hypertension No related anemia Moderate impairment of renal function Urea>36-60 mg% Creatinine clearance (50-74%)	Severe albuminuria Severe hypertension Persistent anemia (<10g%) Severe renal failure Urea >60 mg% Creatinine >4.0 mg% Creatinine clearance <50%	Malignant hypertension Uremic coma/Urea >100%	
BLADDER	None	Slight epithelial atrophy Minor telangiectasia (microscopic hematuria)	Moderate frequency Generalized telangiectasia Intermittent macroscopic hematuria	Severe frequency and dysuria Severe generalized telangiectasia (often with petechiae) Frequent hematuria Reduction in bladder capacity (<150 cc)	Necrosis/ Contracted bladder (capacity <100 cc) Severe hemorrhagic cystitis	
BONE	None	Asymptomatic No growth retardation Reduced bone density	Moderate pain or tenderness Growth retardation Irregular bone sclerosis	Severe pain or tenderness Complete arrest of bone growth Dense bone sclerosis	Necrosis/ Spontaneous fracture	

JOINT	None	Mild joint stiffness Slight limitation of movement	Moderate stiffness Intermittent or moderate joint pain Moderate limitation of movement	Severe joint stiffness Pain with severe limitation of movement	Necrosis/ Complete fixation	