TITLE: A PILOT STUDY OF STEREOTACTIC BODY RADIOTHERAPY (SBRT) IN OLIGOMETASTATIC RENAL CELL CARCINOMA

Principal Investigator:

Stanley Liauw, M.D.
Department of Radiation and Cellular Oncology
University of Chicago Medical Center
5758 S Maryland Avenue MC 9006
Chicago, IL 60637
Phone: (773) 702-6870
Fax: (773) 834-7340
sliauw@radonc.uchicago.edu

Sub-Investigators:

Radiation Oncology
Steven Chmura, MD PHD
Renuka Malik, MD
Ralph Weichselbaum, MD

Urology
Scott Eggener, MD
Arieh Shalhav, MD
Norm Smith, MD

Medical Oncology
Chadi Nabhan, MD
Walter Stadler, MD
Russell Szmulewitz, MD
David Vanderweele, MD

Biostatistics
Theodore Karrison, PhD

Research and Nursing Support
Fauzia Arif
Denise Cloutier, RN

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Intervention: Stereotactic Body Radiotherapy to all sites of disease

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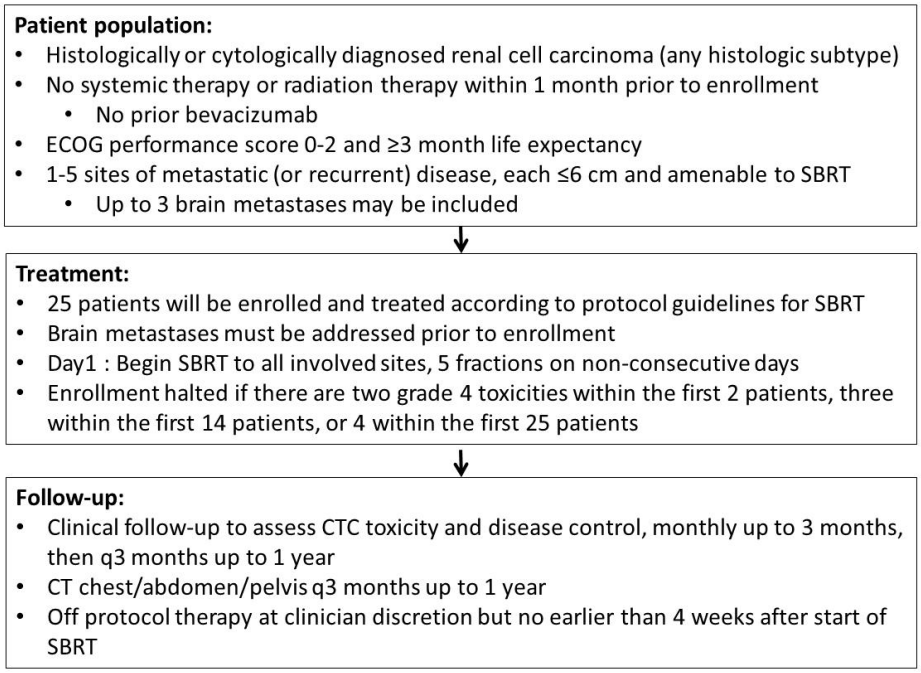
STUDY SUMMARY

SCHEMA



Required Sample Size: 25 patients would be required
Study Center: University of Chicago Medical Center, Chicago, IL

Concept and Rationale: Patients with metastatic renal cell carcinoma (RCC) have a poor prognosis with median survival between 6-15 months, as few patients have a lasting response to cytokine therapy or targeted agent therapy. However, not all patients present with widely metastatic disease. There may be a select group of patients with "oligometastatic" disease—a limited number of metastatic lesions that can be treated with curative intent using aggressive local and systemic therapy. Randomized studies suggest a benefit of cytoreductive surgery in the setting of cytokine therapy, and retrospective series suggest an improvement in survival with metastasectomy. These studies argue that aggressive local therapy to all known sites of disease can yield benefit in the properly selected patient.

However, not all lesions are amenable to surgical resection, and surgery can be associated with significant morbidity. Stereotactic Body Radiotherapy (SBRT) is a method of treatment which directs ablative doses of radiotherapy to the target lesion while limiting radiation to surrounding structures. There is an increasing body of evidence supporting a role for SBRT in oligometastatic cancers throughout the body. A prior Phase I trial at the University of Chicago suggested that a 3-fraction regimen is tolerable in oligometastatic cancer. However, this study included a heterogeneous cohort of patients with multiple primary malignancy types; only 13% of the patients in the trial had RCC. Furthermore, variable radiation doses were prescribed to different sites, complicating the applicability of findings to the clinical setting. Conclusions are therefore more difficult to make regarding the tolerability of SBRT in RCC.

We hypothesize that 5-fraction SBRT with a more uniform dose approach (by having a preferred SBRT dose that is similar for all sites of involvement) in the management of oligometastatic RCC is feasible, not associated with excess toxicity, and can be safely delivered prior to systemic therapy. Information gathered from this study will contribute towards the development of a larger, phase II Chicago consortium study.

Primary Objective: To establish that patients can be treated with 5-fraction SBRT to all sites of metastatic disease with a low (<16%) rate of severe (grade 4) toxicity.

Secondary Objectives:

1. To determine the toxicity profile of SBRT.
2. To determine the feasibility of delivering 5-fraction SBRT per protocol based on proposed normal tissue constraints in a variety of organ sites. (i.e., the ability to treat >80% of enrolled patients according to protocol guidelines).
3. To describe treated lesion control (LeC), progression free survival (PFS), and patterns of failure.
4. To determine the feasibility of accrual and adequacy of eligibility criteria by defining the proportion of eligible cases of metastatic RCC presented at the weekly multidisciplinary genitourinary conference at the University of Chicago Medical Center.
5. To make a preliminary evaluation regarding potential biomarkers in patient serum which may be assessed in a follow-up study (e.g. genetic or immunologic biomarkers).

Study Design: This is a single-armed pilot study to estimate the rate of CTCAE v4.0 grade ≥4 RT-related toxicity of 5-fraction SBRT in patients with oligometastatic RCC. Eligible patients must have histologically or cytologically diagnosed RCC with 1-5 sites of metastases, including up to 3 brain metastases. Patients may present with metastatic disease, or have previously treated primary disease with metastatic recurrence. All sites of metastasis must be ≤6 cm, and patients with recurrent/unresected primary tumors are eligible as long as said tumor is ≤10 cm and there is a plan to treat the primary tumor with a local therapy. Patients may not have had any oncologic therapy within 1 month prior to enrollment, no prior history of bevacizumab, and any brain metastases must be address with surgery and/or radiotherapy prior to enrollment. Patients will be treated with SBRT (preferred dose 50 Gy/5 fractions) to all radiographic sites of gross disease, including the primary if it can not be addressed with non-radiotherapeutic local therapy. Patients can thereafter begin off-protocol systemic therapy per medical oncology discretion, but any therapy will occur no earlier than 2 weeks after completion of RT.

The first 10 patients enrolled on the study will be considered the "initial cohort." If ≥3 of these patients have a CTCAE v4.0 grade ≥4 RT-related toxicity, enrollment will be discontinued and the trial stopped, otherwise 5 additional patients will be accrued. Study investigators will determine whether treatment related toxicities are RT-related or non-RT-related.

Statistical Methods:

Definition of primary outcome/endpoint: RT-related grade ≥4 toxicity will be determined on a case-by-case basis by the study group, taking into consideration the region treated with SBRT, timing of the toxicity, and the nature of the toxicity. Toxicities will be graded as per CTCAE v4.0 criteria.

Definition of secondary outcomes/endpoints: LeC will be defined as absence of clinical or radiographic progression per RECIST criteria. PFS will be defined as progression in the treated lesion, organ in which the treated lesion is present, distant failure, or death from any cause.

Analytic plan for primary objective: Rates of RT-related grade ≥4 toxicity will be recorded, time to RT-related grade ≥4 toxicity will be recorded, and freedom from RT-related grade ≥4 toxicity will be determined using the Kaplan-Meier method.

Analytic plan for secondary objectives: LeC and PFS will be estimated at 1 year using the Kaplan-Meier method.

Sample size justification: A sample size of 25 patients will be needed to assess the safety and appropriateness of this method, identify the optimal candidates, and optimal SBRT fractionation/dose for different clinical scenarios.

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1. OBJECTIVES

1.1. Primary Objective

To establish that patients can be treated with 5-fraction SBRT to all sites of metastatic disease with a low (<16%) rate of severe (grade 4) toxicity.

1.2. Secondary Objectives

1.2.1 To determine the toxicity profile of SBRT.

1.2.2 To determine the feasibility of delivering 5-fraction SBRT based on proposed normal tissue constraints in a variety of organ sites. (i.e., the ability to treat >80% of enrolled patients according to protocol guidelines).

1.2.3 To describe treated lesion control (LeC), progression free survival (PFS), and patterns of failure.

1.2.4 To determine the feasibility of accrual and adequacy of eligibility criteria by defining the proportion of eligible cases of metastatic RCC presented at the weekly multidisciplinary genitourinary conference at the University of Chicago Medical Center.

1.2.5 To make a preliminary evaluation regarding potential biomarkers in patient serum which may be endpoints in a follow-up study (e.g. genetic or immunologic biomarkers).

2. BACKGROUND

2.1 Metastatic Renal Cell Carcinoma

Between 20-33% of patients with renal cell carcinoma (RCC) present with metastatic disease, and of patients with initially limited disease who undergo radical nephrectomy, approximately 25% will ultimately develop metastases [1, 2]. Most patients receive systemic therapy with cytokine therapy or molecularly targeted agents blocking the Vascular Endothelial Growth Factor (VEGF) pathway or mammalian target of rapamycin (MTOR). Despite these interventions, the response rate to systemic therapy is low, with 5-20% responding to cytokine agents and approximately 30-50% to small molecule receptor tyrosine-kinase VEGF inhibitors such as sunitinib and pazopanib [3-8]. Responses are generally of short duration and the median overall survival is typically between 6-15 months [8].

2.2 Oligometastasis

Not all patients with cancer present with widely metastatic disease, and there may be a select group of patients with a more indolent disease course. A select cohort of patients develops a limited number of metastatic lesions, and can potentially be treated with curative intent using aggressive local and systemic therapy [9, 10]. Hellman and Weichselbaum described the existence of an intermediate state in the development of metastatic disease described as oligometastasis [11] – a state where a patient may have a malignancy limited to only a few sites and regions, suggesting an underlying biology not yet capable of widespread metastasis.

The benefit of aggressive resection of metastatic tumors in patients with a limited number and sites of disease has been shown in various malignancies. In patients with metastatic colorectal cancer to the liver, there appears to be a benefit in survival for patients with favorable clinical factors who undergo resection of a limited number of liver metastases, and this approach can produce 5 year overall survival rates between 25-60% [12-16]. Patients with limited pulmonary metastases may have a similar benefit [17]. Similarly, patients with pulmonary metastases from soft tissue sarcoma may have 5 year overall survival rates of approximately 25% when they undergo resection of lung metastases [18-22].

For patients with metastatic RCC, there has been increasing use of cytoreductive nephrectomy prior to systemic therapy. Two randomized studies comparing immediate Interferon-alpha to initial cytoreductive nephrectomy followed by Interferon-alpha showed a benefit in time to progression and median survival in patients who underwent maximal cytoreduction of the primary tumor followed by adjuvant interferon alpha therapy [23, 24]. For patients treated with molecularly targeted agents, a multicenter retrospective series of 314 patients undergoing anti-VEGF therapy showed cytoreductive nephrectomy prior to systemic therapy improved overall survival (19.8 months vs. 9.4 months) [25]. An analysis of patients on a prospective open label, expanded access trial of sunitinib revealed that patients who had nephrectomy prior to sunitinib had a 9.8 month PFS, compared to 6 months for those who did not [26]. The Phase III CARMENA trial is currently assessing the role of cytoreductive nephrectomy prior to sunitinib therapy, and the SURTIME trial is assessing the appropriate timing of surgery in relationship to sunitinib therapy [27, 28].

In addition to resection of the primary tumor, many advocate removal of metastatic lesions in patients with a limited number of lesions of RCC. A retrospective study of 278 patients with metastatic RCC from Memorial Sloan-Kettering Cancer Center showed that patients who underwent surgical resection of metastatic lesions had an improved 5 year overall survival (44% vs. 11%) [29]. Additionally, the survival of patients after their second or third resection was not significantly lower. Eggener et al. reviewed 129 patients with recurrent and metastatic renal cell carcinoma. 34% of patients underwent metastasectomy, which was associated with a survival benefit [30]. Alt et al. reviewed 125 patients who underwent metastasectomy compared to 762 patients who did not. Complete metastasectomy was associated with improved cause-specific survival (median 4.8 vs. 1.3 years, $p< 0.001$). The benefit was present for both synchronous or asynchronous multiple metastases [31]. These data suggest that in a select group of patients, local eradication of metastatic lesions and unresected primary tumors may have a benefit in the survival of patients with metastatic RCC.

2.3 Stereotactic Body Radiotherapy in Oligometastasis

However, nephrectomy and metastasectomy are invasive procedures with risk for perioperative morbidity. This is particularly the case for patients having comorbid conditions or requiring more extensive surgeries. Also, not all patients are candidates for resection due to invasion of adjacent structures by tumors. Radiotherapy is an alternative modality used for the treatment of radiographically visible tumors. Although RCC has historically been thought to be resistant to conventionally fractionated radiotherapy (1.8-2 Gy per fraction) [32-34], multiple series suggest it may be sensitive to higher fraction sizes of radiotherapy (stereotactic radiotherapy) [35-38].

Stereotactic Radiotherapy is the use of high doses of radiation per fraction to deliver ablative doses of radiation to lesions throughout various body sites. Stereotactic radiotherapy administered in one fraction, commonly to intradural lesions, is usually described as stereotactic radiosurgery (SRS). Stereotactic radiotherapy administered over 1-5 fractions to extracranial sites in > 5 Gy per fraction is known as stereotactic body radiotherapy (SBRT).

There is considerable experience with SBRT in medically inoperable early stage lung

cancers [39-42], and an increasing body of evidence suggesting a role of SBRT in oligometastatic cancers. The ablative doses of SBRT in the oligometastasis setting have allowed for local control rates approaching 90% in such series [43-46].

Based on retrospective series suggesting a local control rate with SBRT of 87-98% [35, 47-49], a prospective Phase II Swedish study assessed the role of SBRT in 30 patients with metastatic or inoperable primary tumor RCC [38]. Patients were treated with 20-50 Gy given in 2-5 fractions to involved sites. With median follow-up of 52 months, 21% of patients had complete regression of tumor, 31% had a partial response, and 27% had stable radiographic size. The rate of local control for all treated lesions was 98%, and the overall survival for the entire cohort was 32 months. This suggests SBRT can be effective to control RCC. Additionally, retrospective series also suggest limited toxicity with SBRT [37, 45, 47, 49-51].

There are numerous SBRT fractionation regimens that have been evaluated [38, 39, 41, 52-54]. However, the optimal dose and number of fractions of SBRT are unknown. A prior phase I dose escalation trial was performed to evaluate SBRT for oligometastatic cancer at the University of Chicago. This study used a modified Fibonacci dose escalation to identify the maximal safe organ-specific doses that could be delivered in a 3-fraction SBRT regimen [45]. However, the patient cohort in this study was heterogeneous, with only 8 of 61 patients (13%) having renal cell malignancies. Additionally, different doses for each specific organ of involvement were used. This approach is more complex and may be more difficult to implement in subsequent trials and in the community. In addition, 5-fraction SBRT may be better tolerated by critical structures, particularly for tumors near gastrointestinal critical structures. For primary tumors, Wersall et al used 40 Gy in 5 fractions for tumors up to 10 cm in size [47]. Videtic et al evaluated the use of a SBRT regimen of 50 Gy in 5 fractions in medically inoperable non-small cell lung cancer and found a 3 year local control rate of 94.4% and acceptable toxicity [41]. In addition, 50 Gy in 5 fractions is the starting dose and fractionation of RTOG 0813, a Phase I/II dose escalation study of SBRT in non-small cell lung cancer currently open in multiple centers. Typically, the dose and fractionation schemas used to treat metastatic lesions in the lung are similar to those used in primary lung cancer. The 50 Gy in 5 fractions schema also has the benefit of being tolerable in multiple organ sites other than the lungs [55]. Thus, 50 Gy in 5 fractions was selected as the preferred schema in our trial, with 40 Gy in 5 fractions used as an alternative dose when normal tissue constraints cannot be met using the preferred dose.

Most series suggest a favorable risk profile of SBRT when keeping doses to normal tissues within established dose constraints. However, there are a few case reports of patients treated with radiotherapy (both SBRT and conventionally fractionated radiotherapy)[56-60]. The agent that appears to be most commonly associated with severe toxicity is bevacizumab; several larger series have demonstrated safety when combining tyrosine kinase inhibitors (e.g. Sunitinib, Pazopanib) with radiation therapy [61-64]. Therefore, this study will exclude men treated with bevacizumab prior to enrollment, but will allow patients treated with other tyrosine kinase inhibitors to be eligible for this trial.

2.4 Rationale for current study

The above evidence suggests a role for aggressive local treatment of metastatic lesions in RCC. We hypothesize that SBRT can be safely and effectively delivered in patients with oligometastatic RCC. Results will inform the development of a larger, multicentric trial.

This study will evaluate a 5-fraction regimen in patients who have a histology diagnosis of metastatic RCC with 5 or fewer sites of disease. All organs of involvement will receive 5 fractions with a preferred dose of 50 Gy in 5 fractions. This pilot study will evaluate the ideal candidates for this approach, the likely accrual and accrual rate of a phase II study, and the optimal dosimetric and dose/fractionation considerations in pursuing this approach. In addition, this study will allow for the collection of data to possibly refine eligibility and treatment

delivery for future studies, and help determine sample size calculations for the next generation trials. Subsequent testable hypotheses could include randomized comparisons of SBRT +/- concurrent molecularly targeted systemic therapy, observation +/- SBRT, or systemic therapy +/- SBRT.

2.4.1 Rationale for Secondary Objectives

Patients with sites of metastatic disease commonly present with pain from these lesions. Conventional radiotherapy can offer palliation for most patients, but the durability of pain control is variable. In order to describe the clinical efficacy of this treatment approach, we will also evaluate objective response rate, treated lesion control, and the patterns of failure.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed metastatic or recurrent RCC (any histologic subtype).

3.1.2 Patients must have between 1 to 5 new or recurrent lesions suspicious for metastatic RCC on diagnostic imaging.

3.1.2.1 Each extracranial lesion must be ≤ 6 cm and amenable to SBRT or surgical excision.

3.1.2.2 Patients must have 3 or fewer brain metastases, of size ≤4 cm.

3.1.2.2.1 Brain metastases must be treated prior to enrollment in the study. The modality of treatment of brain metastases can include surgical resection, whole brain radiotherapy, stereotactic radiosurgery, or any combination of the above.

3.1.2.3 Patients who have an intact unresected primary tumor should be considered for radical nephrectomy and primary resection prior to enrollment in the study. If the patient is not eligible for surgical resection, the primary tumor must be amenable to SBRT or RFA. Generally, this will be defined as a primary tumor <10 cm in size or a primary lesion which can be treated to a dose of ≥8 Gy x 5 without excessive perceived risk of toxicity.

3.1.3 Patients must have had at least a CT of the chest, abdomen, and pelvis within 4 weeks of registration in the trial. CT or MRI of the brain is only required in the presence of neurologic symptoms.

3.1.4 Patients must have had no radiotherapy, immunotherapy, chemotherapy or therapy with targeted agents within the last 1 month.

3.1.5 Patients may not have had prior bevacizumab, based on case reports of tracheo-esophageal fistula in patients treated with bevacizumab and radiotherapy [58, 59].

3.1.6 Age ≥18 years. Because of the risk of adverse events in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric SBRT trials.

3.1.7 ECOG performance status ≤2 (see Appendix A).

3.1.8 Life expectancy of ≥3 months.

3.1.9 Patients must have normal organ and marrow function within 30 days of registration, as defined below:

– absolute neutrophil count	≥500/mcL
– hemoglobin	≥ 8.0 g/dL
– platelets	≥50,000/mcL
– total bilirubin	within normal institutional limits
– AST(SGOT)/ALT(SGPT)	≤3X institutional upper limit of normal if liver metastases are present

3.1.10 Women of childbearing potential must have a negative pregnancy test within 14 days of registration.

3.1.11 Patients must have the ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients who have had prior chemotherapy, immunotherapy, targeted therapy, or radiotherapy within 1 month of enrollment.

3.2.2 Patients who have had any prior bevacizumab, due to case reports suggesting a possible risk of severe toxicity in combination with radiotherapy [58, 59].

3.2.3 Patients with radiographic or clinical findings of spinal cord compression or cauda equina syndrome with neurologic deficit thought to be due to malignancy.

3.2.4 Patients may not be receiving any systemic anti-cancer agents or other investigational agents during radiation therapy.

3.2.5 Patients may not have received prior radiation therapy to a site of recurrence which would require overlap of appreciable radiation dose.

3.2.6 Known active invasive malignancy except for renal cell carcinoma and/or non-melanoma skin cancer.

3.2.7 Severe, active co-morbidity, defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months prior to registration;
- Transmural myocardial infarction within the last 6 months prior to registration;
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
- Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy _within 30 days prior to registration;
- Severe hepatic disease, defined as a diagnosis of Child-Pugh Class B or C hepatic disease if the liver is involved with metastatic disease;
- HIV positive with CD4 count < 200 cells/microliter. Note that patients who are HIV positive are eligible, provided they are under treatment with highly active antiretroviral therapy (HAART) and have a CD4 count ≥ 200 cells/microliter within 30 days prior to registration. Note also that HIV testing is not required for eligibility for this protocol;

3.2.8 Pregnancy or women of childbearing potential who are sexually active and not willing/able to use medically acceptable forms of contraception during protocol treatment or for at least 6 months following treatment; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 Patient Recruitment

Patients will be identified and recruited through Radiation Oncology, Urology, and Medical Oncology clinic consultations and follow-up visits at the University of Chicago

4.2 Patient Renumeration

Patients will receive no payment for participation in this trial.

5. TREATMENT PLAN

5.1 Study Design

This is a pilot study of the use of SBRT to all sites of disease for patients with oligometastatic RCC. Patients may receive off-protocol systemic therapy per medical oncologist discretion no earlier than 4 weeks after starting SBRT. While there are no restrictions on systemic therapy following SBRT, caution is advised on the use of bevacizumab given prior case reports demonstrating the possibility of heightened toxicity when this agent is used in the setting of SBRT. Limited or symptomatic recurrences can also be treated with radiation therapy (either SBRT or conventional therapy) at the clinician's discretion.

Enrollment will proceed according to a sequential toxicity monitoring schema to test the null hypothesis of a π_0=5% grade 4 toxicity rate against an upper acceptable boundary of a π_1=20% grade 4 toxicity rate. Trial enrollment will be halted if there are two grade 4 events within the first 2 patients, if there are three events within the first 14 patients, or if there are four events within the first 25 patients. The treatment will be considered successful if there are less than four events in 25 evaluable patients (<16%).

Treatment will be administered on an outpatient basis. The details of planning and administration of radiotherapy are discussed in detail in section 6. Reported adverse events and potential risks for SBRT are described in Section 8. Appropriate dose modifications for SBRT are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

The pilot study will be considered successful if 25 patients are accrued, with less than 4 having Grade 4+ toxicity events after SBRT.

5.2 Definition of Grade ≥4 RT-related Toxicity

The evaluation period of acute toxicity will be defined by the period of 90 days following the first fraction of RT. Of note, late grade ≥4 toxicity occurring beyond 90 days and through the one year of planned post-treatment follow-up will still have the ability to modify the trial design and accrual per the discretion of the primary investigator. Grade ≥4 toxicity will be defined

according to Common Toxicity Criteria version 4.0 (ctep.cancer.gov/reporting/ctc.html). Toxicities will be classified by a study committee as likely due to SBRT or non-radiotherapy-related based on review of nature of toxicity and the areas being treated with radiotherapy.

5.3 General Concomitant Medication and Supportive Care Guidelines

Patients may receive non-chemotherapeutic agents for premedication and supportive care as per the standard of care while on study.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse events, radiotherapy should be completed within 1 month of the first day of radiotherapy (Day 28 of protocol treatment). Patients may receive systemic therapy off-protocol no earlier than 4 weeks after starting SBRT.

5.5 Duration of Follow Up

Patients will be followed for 1 year after beginning radiotherapy. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.6 Criteria for Removal from Study

Patients will be removed from study when one of the following criteria applies:

- Intercurrent illness that prevents administration of SBRT,
- Unacceptable adverse event(s),
- Death,
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator/treating physician.

The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. RADIATION THERAPY

6.1 Simulation

6.1.1 SBRT

6.1.1.1 Patient Positioning

Patients must be simulated in a stable, supine position capable for reproducibility of positioning at the time of treatment, to allow for the patient to feel as comfortable as possible. A prone position is not allowed. A variety of immobilization systems may be utilized with reference to the treatment delivery coordinate system.

6.1.1.2 Simulation

CT simulation will be performed with proper patient positioning and immobilization. CT will be the primary image platform for treatment planning. The use of intravenous contrast is recommended if it can help delineate the tumor or normal tissues (e.g. for liver metastases). Additionally, oral, rectal, or bladder contrast are recommended if these agents will improve tumor or target delineation.

When available, 4D CT should be used for all sites where there is concern for movement due to normal respiration.

6.2 Premedications

No premedications are required for any aspect of radiotherapy, however corticosteroid, anti-emetic, anti-anxiety, and narcotic/non-narcotic pain medications are allowed per physician discretion.

6.3 Target Volumes

When available, imaging studies such as MRI and PET are may be fused with planning CT to aid contouring of the target volumes.

6.3.1 Target Definition

6.3.1.1 The definition of volumes will be in accordance with the ICRU Report 62: Prescribing, Recording and Reporting Photon Beam Therapy. [65]

6.3.1.2 A gross tumor volume (GTV) will be entered for each lesion, based on available imaging data.

6.3.1.3 In the absence of respiratory gating, for any lesion that is subject to movement from respiration, an internal target volume (ITV) will be defined as the volume that accounts for intrafraction target motion.

6.3.1.4 A clinical target volume (CTV) will be defined as the GTV or ITV (when available) plus a margin for microscopic extension.

6.3.1.5 A planning target volume (PTV) will be determined which will correspond to CTV plus appropriate margin for tumor motion and set-up uncertainty.

6.3.1.6 Separate GTV, CTV, PTV, and if applicable, ITV contours, will be created for all sites of gross disease.

6.4 Treatment Planning

6.4.1 3D coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. The treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose volume histogram of the PTV and normal structures. 3D “forward” planning or “inverse” planning with beamlet intensity modulated treatment planning are allowed.

6.4.2 Respiratory gating is strongly recommended if there is significant movement of the GTV with respiration.

6.4.3 Treatment is to be delivered using a linear accelerator and photon energies ≥ 6 MV.

6.4.4 Corrections will be made to account for tissue heterogeneity.

6.4.5 Any dose > 110% must be within the PTV.

6.5 Dose Specifications

Doses will be prescribed to the PTV. The PTV may be covered by a lower isodose line than usually used in conventional radiotherapy planning, ranging from 60-100%. Ideally, the prescription dose will cover >90% of the GTV (V100 GTV > 90%, and V95PTV > 90%). Hot spots within the PTV are allowed, unless the PTV also overlaps an organ at risk. A lower coverage goal will be acceptable if necessary to meet normal tissue constraints, which will be assigned priority over tumor coverage.

6.5.1 SBRT

At all dose levels in dose escalation, the preferred SBRT dose is 50 Gy in 5 fractions of 10 Gy to all sites of disease, including the primary tumor if it can not be treated with surgical resection or alternative local therapy. However, normal tissue constraints are of priority in selecting the prescribed dose, and if the dose to normal tissues exceeds the normal tissue dose constraints, then dose can be de-escalated to a lower dose, such as 8 Gy x 5. One site in which de-escalation is routinely expected includes the treatment of vertebral body metastases, in which the preferred SBRT dose is 27-30 Gy in 3 fractions of 9-10 Gy.

5.6 Critical Structures

6.6.1 Critical structure dose constraints are per Table 1. These dose constraints are based on NRG BR002, a NRG Oncology cooperative group prospective Phase I clinical trial of SBRT for the treatment of multiple metastases in patients with oligometastatic cancer.

Table 1: Normal tissue critical structure dose constraints

Serial Organ	Volume	Dose (Gy)	Avoidance Endpoint
Spinal Cord	<0.03 cc	28	Myelitis
	<0.35 cc	22	Myelitis
	<1.2 cc	15.6	Myelitis [66]
Ipsilateral Brachial Plexus	< 0.03 cc	32	Brachial Plexopathy (RTOG 0813)
	<3 cc	30	Brachial Plexopathy (RTOG 0813)
Cauda Equina	<0.03 cc	32	Neuritis (AAPM TG-101)
	<5 cc	30	Neuritis (AAPM TG-101)
Sacral Plexus	<0.03 cc	32	Neuropathy (AAPM TG-101)
	<5 cc	30	Neuropathy (AAPM TG-101)
Trachea and Ipsilateral Bronchus (Non-adjacent wall)	<0.03cc	40	Stenosis/Fistula
	<5cc	32	Stenosis/Fistula (RTOG 0813)
Esophagus* (Non-adjacent wall)	<0.03cc	35	Stenosis/Fistula [66]
	<5 cc	27.5	Stenosis/Fistula (RTOG 0813)
Heart/Pericardium	<0.03 cc	38	Pericarditis [66]
	<15 cc	32	Pericarditis (RTOG 0813)
Great vessels (Non-adjacent wall)	<0.03 cc	53	Aneurysm [66]
	<10 cc	47	Aneurysm (RTOG 0813)
Skin	< 0.03cc	38.5	Ulceration
	< 10cc	36.5	Ulceration
Stomach	< 0.5cc	35	Ulceration/Fistula
	< 5cc	26.5	Ulceration/Fistula
Duodenum*	< 0.5 cc	30	Ulceration (RTOG 1112)
	< 5 cc	18.3	Ulceration [67]

Jejunum/ileum*	< 0.03 cc	32	Ulceration
	< 30cc	20	Enteritis/Obstruction
Bowel*	< 0.03 cc	40	Ulceration
	<20 cc	28.5	Colitis/Fistula
Rectum*	<0.03 cc	55	Ulceration
	<3.5 cc	50	Proctitis/Fistula
	<20 cc	32.5	Proctitis/Fistula
Bladder	< 0.03	38	Cystitis/Fistula
	<15 cc	20	Cystitis/Fistula
Ureter	<0.03 cc	45	Stenosis
Penile Bulb	<3 cc	30	Impotence [66]
Femoral head	<10 cc	30	Necrosis
Bile Duct	<0.03 cc	41	Stenosis
Renal hilum/Vascular Trunk	<15 cc	23	Malignant Hypertension
Rib	<0.03 cc	57	Pain or Fracture
	<5 cc	45	Pain or Fracture
Parallel Organ	**Volume**	**Dose (Gy)**	**Avoidance Endpoint**
Lung (total)	< 37% lung volume	13.5	Pneumonitis
	< 1500 cc	12.5	Basic Lung Function (RTOG 0813)
	< 1000 cc	13.5	Pneumonitis (RTOG 0813)
Ipsilateral Kidney	< 130 cc	14.5	Basic Renal Function
Total Kidney	< 200cc	18	Basic Renal Function
Liver	<700 cc	21	Liver Function [66]

*Note: avoid circumferential irradiation.

Dose volume histograms (DVHs) will be constructed to assess dose to PTV and normal tissue structures. The pertinent critical structure dose constraints will be determined by the location of the treated lesion. These must be met prior to plan approval, otherwise target coverage, or prescription dose, must be decreased to meet the constraints as above.

6.6.2 Critical Structure contouring

In order to verify each of these limits, the organs must be contoured such that appropriate volume histograms can be generated. The specific critical structures to be contoured and assessed by DVH for each case will be determined by the treating radiation oncologist. Instructions for the contouring of these organs are as follows:

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 5 cm above the superior extent of the PTV and continuing on every CT slice to at least 5 below the inferior extent of the PTV.

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.

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.

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 5 cm above the superior extent of the PTV and continuing on every CT slice to at least 5 cm below the inferior extent of the PTV.

Brachial Plexus
The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamina on the involved side from around C5 to T2. However, for the purposes of this protocol, only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus. This neurovascular complex will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib. If the PTV of all metastases is more than 5 cm away from the brachial plexus, this structure need not be contoured.

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 (aortopulmonary window) and extend inferiorly to the apex of the heart.

Trachea and Proximal Bronchial Tree
The trachea and proximal bronchial tree will be contoured as two separate structures using mediastinal windows on CT to correspond to the mucosal, submucosa and cartilage rings and airway channels associated with these structures. For this purpose, the trachea will be divided into two sections: the proximal trachea and the distal 2 cm of trachea. The proximal trachea will be contoured as one structure, and the distal 2 cm of trachea will be included in the structure identified as proximal bronchial tree.

- *Proximal Trachea*

  Contouring of the proximal trachea should begin at least 5 cm superior to the extent of the PTV for lung metastases or 5 cm superior to the carina (whichever is more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree.

- *Proximal Bronchial Tree*

  The proximal bronchial tree will include the most inferior 2 cm of distal trachea and the proximal airways on both sides as indicated in Figure 6-1. The following airways will be included according to standard anatomic relationships: the distal 2 cm of trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation. If there are parts of the proximal bronchial tree that are within

GTV, they should be contoured separately, as “proximal bronchial tree GTV”, not as part of the “proximal bronchial tree”.

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.

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).

Great Vessels
The great vessels (aorta and vena cava, not the pulmonary artery or vein) will be contoured using mediastinal windowing on CT to correspond to the vascular wall and all muscular layers out to the fatty adventitia. The great vessel should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV. For right sided tumors, the vena cava will be contoured, and for left sided tumors, the aorta will be contoured.

Non-adjacent Wall of a Structure
For the esophagus, trachea and proximal bronchial tree, and great vessels, the nonadjacent wall corresponds to the half circumference of the tubular structure not immediately touching the GTV or PTV, These contours would start and stop superiorly and inferiorly just as with the named structure. The half lumen of the structure should be included in this contour.

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 colon/rectum.

Bowel (Large/Small)
From the ileocecal area to include the ascending, transverse, descending and sigmoid colon as one structure.

Rectum
The entire rectum with contents from the peritoneal reflection of the sigmoid to the anus.

Bladder
This organ will be contoured as bladder wall exclusive of urinary contents

Kidney (renal cortex)
Both the right and left kidney, excluding renal pelvis/collecting system, should be contoured in their entirety (the renal cortex)

Liver
The entire liver minus the GTV targets.

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

Femoral Heads
The ball of the head and socket joint.

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).

Other Structures
The constraints tables above contain other structures. These are required if the structure is within 5 cm of the PTV.

6.7 RT Treatment

6.7.1 Radiotherapy will begin on Day 1 of therapy.

6.7.2 SBRT fractions to each individual site may occur at most 3 times per week, but never on consecutive days.

6.7.3 SBRT fractions to the different sites of involvement may occur on the same day or on different days per patient and physician preference.

6.7.4 All radiotherapy must be completed by Day 28 of radiation, unless an adverse event occurs to delay treatment

6.7.5 Prior to each fraction of SBRT, patients will be brought to the treatment room and placed in the treatment position using custom immobilization. Cone-beam CT prior to administration of fraction to confirm appropriate patient set-up is preferred if available and indicated, but alternatively patients may have pre-treatment KV portal imaging.

6.8 Radiotherapy Adverse Events

Please refer to Section 8 for details regarding radiotherapy adverse events and adverse event reporting.

7. RISKS AND BENEFITS

7.1 RADIOTHERAPY ADVERSE EVENTS

Adverse event (AE) monitoring and reporting will be performed. Please refer to Section 5.2 for definition of Dose Limiting Toxicity.

Radiotherapy reactions will be defined as acute or late as defined below:

Acute Reactions: Acute side effects are considered as occurring ≤ 90 days from the start of radiation therapy. They will be documented using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (ctep.cancer.gov/reporting/ctc.html).

Late Reactions: Late side effects are considered as occurring > 90 days from the start of radiation therapy through a 12 month total evaluation period. They will also be documented using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (ctep.cancer.gov/reporting/ctc.html).

Alopecia, skin hyperpigmentation, and erythema are likely in all treatment fields. It is likely that all patients treated on study will develop some level of fatigue. Rarely, some patients may have a vasovagal response before, during, or after SBRT fractions.

Other side effects of treatment will vary depending on the location of disease and volume of normal tissues in the radiation therapy portals. All attempts should be made to minimize side effects by limiting the normal tissue in the radiation therapy portals and adhering to the normal tissue dose constraints of this study.

7.1.1 Additional Adverse Events Associated with stereotactic radiation to the brain.
Acute Reactions: Expected acute reactions include transient small amounts of bleeding and swelling (including in sites of frame placement for radiosurgery), transient head/neck pain/discomfort, transient nausea and vomiting, and headache. Rare toxicities include infection of stereotactic frame pin sites, intracranial or extracranial hemorrhage, vasovagal response to frame placement.

Late Reactions: Edema of treated lesion is expected on imaging, but this is often asymptomatic. Unlikely toxicities include persistent nausea, vomiting or headache. Rare toxicities include radionecrosis, lethargy, somnolence, damage to the eye with the possibility of blindness, cataracts, severe neuropsychological dysfunction, hearing loss, pituitary dysfunction, cranial neuropathy.

7.1.2 Additional Adverse Events Associated with Head and Neck radiotherapy.
Acute Reactions: Depending on the structure irradiated in the region, possible but expected toxicities include pharyngitis, esophagitis, laryngitis, mucositis, xerostomia, xerophthalmia, voice hoarseness, otic changes, dysgeusia, dysphagia, odynophagia. Other possible but less likely acute reactions include sinusitis, pruritis of external auditory canal, pharyngotympanic dysfunction, mucosal hemorrhage, and weight loss.

Late Reactions: Unlikely toxicities include xerostomia, dental caries, dysgeusia, tracheoesophageal fistula, vascular rupture, hypothyroidism. Cataracts are possible but uncommon. Other possible but rare late effects include damage to the eye with the possibility of blindness, accelerated atherosclerosis, severe neuropsychological dysfunction, damage to spinal cord, brachial plexopathy, symptomatic esophageal stricture.

7.1.3 Additional Adverse Events Associated with Lung/Mediastinal Radiation
Acute Reactions: Cough and esophagitis (if the esophagus is included in the radiation therapy portal) are likely. Severe esophagitis (requiring IV hydration, therapy interruption, or severe cough), shortness of breath, and hemoptysis are possible but less likely.

Late Reactions: Asymptomatic fibrotic changes in the lung seen on chest imaging are likely. Severe pneumonitis or fibrosis of lung resulting in severe respiratory compromise, symptomatic esophageal stricture, radiation pericarditis, and myocardial injury, spinal cord injury, and brachioplexopathy are possible but unlikely side effects of radiation.

7.1.4 Additional Adverse Events Associated with Abdominal/Pelvic Radiation
Acute Reactions: Anorexia, diarrhea, nausea, and vomiting are likely but dependent on the volume of stomach and bowel in the treatment fields. Urinary urgency and dysuria are likely if the bladder is in the radiation therapy fields. Severe nausea, vomiting, and/or diarrhea that requires therapy interruption or IV fluid replacement, abnormal liver function or renal function tests, and low

blood counts are less likely but possible. Pain with defecation and mild to severe rectal bleeding are possible.

Late Reactions: hepatitis, nephritis, bowel obstruction or perforation, radiation cystitis, or proctitis are possible but unlikely. Erectile dysfunction is also unlikely. Damage to spinal cord is possible but unlikely.

7.1.5 Additional Adverse Events Associated with Radiation to the Soft Tissues or Bones in the Extremities

Acute Reactions: Minor skin reactions are likely; moist desquamation is possible but unlikely.

Late Reactions: Swelling of the treated region and poor wound healing are possible but unlikely. Pathologic fracture of the bone, severe debilitating swelling, weakness, and radiation-induced neoplasm are possible but unlikely. Fibrosis of extremity and joints with resulting pain and/or decreased extremity function is possible but unlikely.

7.1.6 Additional Adverse Events Associated with Radiation to the Spine

The possible acute and late toxicities of radiation to the spine will include those that affect radiation to the region of the body in which the spine is being treated (i.e. head and neck, chest, abdomen, pelvis). Additionally, rarely, patients could develop damage to the spinal cord or cauda equina resulting in severe neurologic dysfunction/paralysis.

7.1.7 Treatment of Adverse Events:

All attempts should be made to limit the symptoms and the overall impact of acute and late effects of radiation. Side effects of treatment may be treated per standard of care supportive agents.

8. Adverse Event Reporting

University of Chicago Reporting Guidelines

8.1 If the adverse event requires reporting, the Research Nurse or MD reports the adverse reaction to the Cancer Clinical Trials Office (CCTO) at 773-702-5149 by the end of the business day when he/she becomes aware of the event. Events occurring after business hours will be reported to the CCTO by 12 pm (noon) the next business day.

8.2 The following information is required when calling in the event:

- Caller's Name and Telephone Number
- Patient Initials
- Patient Medical Record Number
- IRB Protocol Number
- PI of Study
- Attending Physician
- Date of Event
- Description of Event (including grade of the event and attribution of the event and if the event required hospitalization)

8.3 E-mail is sent to the research nurse, attending physician and PI of the study informing them that adverse reaction notification has been received.

8.4 The University of Chicago's IRB Serious Adverse Event Form must be sent to the CCTO within **5 calendar days of event occurrence**. The UC IRB Serious Adverse Event form is available on-line at: http://ors.bsd.uchicago.edu/HS/newirbforms. This form must be typed. Once the forms are completed, the original is forwarded to the study PI to review and sign. The signed report is delivered to the QA Coordinator. A weekly report of delinquent or pending documents will be forwarded to the applicable person who reported the event. All delinquent reporting (greater than

10 days from event occurrence) must include documentation of reason for delinquency and may require implementation of an action plan.

8.5 Once the appropriate AE documents have been received, the CCTO forwards these to the IRB. A copy will be forwarded to the appropriate Research Nurse.

9. Data Safety and Monitoring

Data Safety and Monitoring will occur at the weekly University of Chicago GU oncology phase I/II conference meetings, which are lead by senior level medical oncologists. At each meeting, all active studies will be reviewed for safety and progress toward completion. Toxicities and adverse events will be reviewed at each meeting and a Data Safety and Monitoring form will be completed for each protocol and signed by either the Principal Investigator, the Chairman of the Department or by his designate if the Chairman is not available.

10. STUDY CALENDAR

Baseline CBC, serum chemistry, and pregnancy test (if indicated) are to be conducted within 30 days prior to study registration. Scans and x-rays must be done <u><6</u> weeks prior to study registration.

	Pre-Study	Wk 1	Wk 2	Wk 3-4	1 Mo Post-RT^	2 Mo Post-RT^	3 mo Post-RT^	6 mo Post-RT^	9 mo Post-RT^	1 yr Post-RT^
Radiotherapy		R	R	(R)						
Informed Consent	X									
Medical History	X	X	X	X	X	X	X	X	X	X
Concurrent meds	X	x	X	X	X	X	X	X	X	X
Adverse Events evaluation		X	X	X	X	X	X	X	X	X
Clinic Visit	X	X	X	X	X	X	X	X	X	X
Pain Assessment	X	X	X	X	X	X	X	X	X	X
CBC/platelets	X	X*			X*		X*			
Serum chemistry[a]	X	X*	X*	X*	X*		X*	X*	X*	X*
Plasma#	X						X	X		X
Radiographic imaging[b]	X						X	X	X	X
B-HCG[c]	X									

^: Date of post-treatment visit will correspond to the start date (first day) of SBRT
R: Radiotherapy: 10 Gy x 5 fractions, or maximum safe dose to all extracranial sites, and size based SRS
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: CT of the head, chest, abdomen, and pelvis, and any other pertinent imaging based on clinical situation are required within 28 days of each visit.
c: Serum pregnancy test (women of childbearing potential)
*: CBC and serum chemistry may be obtained per physician discretion following initial assessment. However, it is required to check AST and ALT if SBRT is delivered to liver, at each week of RT, at 1 month post-RT, and at each q3 month follow-up interval (3, 6, 9, 12 months post-RT).
#: For patients who provide consent

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effects and Endpoints

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated at follow-up visits within one month of completion of radiotherapy, and then subsequently every 3 months for one year. CT of the chest, abdomen, and pelvis, and any other pertinent imaging (e.g. CT or MRI head for brain metastases) are required within 28 days of each follow-up visit.

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [68]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

11.1.1 Definitions

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

Evaluable for objective response. Patients who have had their disease re-evaluated following completion of radiotherapy will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

11.1.2 Disease Parameters

Target lesions. All lesions which are visible on imaging prior to SBRT and are targets for radiotherapy will be considered target lesions and should be recorded and measured at baseline.

Non-target lesions. Any metastatic lesions that arise in follow-up imaging after completion of radiotherapy which were not target lesions for the initial radiotherapy. These sites of relapse are not required to receive treatment with SBRT, but may be treated at the discretion of the treating clinician. The treatment may be palliative or locally aggressive, and is not subject to the guidelines of the radiation treatment parameters described in section 6.

11.1.3 Methods for Evaluation of 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 study enrollment and treatment and never more than 4 weeks before study enrollment.

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.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI: These techniques should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed using a ≤5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions will occur to determine lesion control at each CT scan evaluation. Local control will be defined as the lack of progressive disease based on the criteria below:

Complete Response (CR):	Disappearance of target lesion
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesion, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesion, taking as reference the smallest sum LD recorded since the treatment
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

11.1.4.2 Evaluation of Non-Target Lesions

By definition, the appearance of new non-target lesions following completion of radiotherapy will be considered overall progressive disease.

If for any reason the response of non-target lesions to systemic therapy is needed, the same criteria as those for target lesions will be used for Complete Response, Partial Response, Progressive disease, and Stable disease for each individual non-target lesion during follow-up evaluations.

11.1.5 Endpoint Definitions

Duration of treated lesion control
Duration of time from start of treatment to the time of local progression at each treated lesion. Local progression is defined as any progressive disease as judged by RECIST criteria of treated lesions

Organ-specific control
Duration of time from start of treatment to the time of development of a new lesion on imaging within an organ in which a lesion was treated with SBRT.

Progression-free survival
Duration of time from start of treatment to time of progression. Progression is defined as any new sites of disease on imaging or any progressive disease by RECIST criteria at initially treated sites of disease (within 80% isodose line).

11.2 Dosimetric description of delivery of Radiotherapy

Radiation plans, target volumes, and DVHs will be reviewed to assess for acceptable doses based on site and normal tissue toxicity dose constraints. Descriptive statistics will be calculated for each dose cohort to characterize these dosimetric parameters. The relationship between grade of toxicity and dose parameters will also be described.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

This is a pilot study of the use of 5-fraction SBRT for oligometastatic RCC. Patients enrolled in the study will be treated with SBRT to all sites of disease. Enrollment will proceed according to a sequential toxicity monitoring schema [69] to test the null hypothesis of a π_0=5% grade 4 toxicity rate against an upper acceptable boundary of a π_1=20% grade 4 toxicity rate. Trial enrollment will be halted if there are two grade 4 events within the first 2 patients, if there are three events within the first 14 patients, or if there are four events within the first 25 patients. The treatment will be considered successful if there are less than four events in 25 patients, i.e., <16% observed toxicities. This design has approximately 80% power (78.8%) to declare the treatment too toxic if the true grade 4 toxicity rate is π_1=20%.

Patients will be followed for a total of one year after completion of the trial per protocol. Patients may be treated with off-protocol systemic therapy no earlier than 2 weeks after completion of RT. The primary endpoint is the rate of grade 4 RT-related toxicity with this treatment approach. Secondary endpoints include determining the toxicity profile of 5-fraction SBRT, determining the feasibility of 5-fraction SBRT based on normal tissue dosimetric constraints based on the organ site of involvement, describing the LeC, PFS, and patterns of failure of this approach, as well as to explore the feasibility of accrual and the adequacy of the eligibility criteria of this approach.

12.2 Sample Size/Accrual Rate

The maximum sample size will be 25 evaluable patients according to the schema above. This sample size is needed in order to signify feasibility of this disease approach and accrual to a larger, later phase trial.

12.3 Stratification Factors

Patients will be stratified by the number of lesions and presence/absence of brain metastasis; index lesions will be stratified by the size and location.

12.4 Analysis of the Primary Endpoint

The primary endpoint is the rate of grade ≥4 RT-related toxicity with this treatment approach. RT-related toxicity will be recorded as specified in the study calendar (section 10). All toxicity will be determined to be RT-related or non-RT-related by the study committee.

12.5 Analysis of Secondary Endpoints

The secondary endpoints of this study include determining the toxicity profile, LeC, and patterns of failure of this approach, as well as the feasibility of a 5-fraction SBRT regimen based on normal tissue dose constraint and treatment goals, and the feasibility of accrual to an oligometastasis trial in RCC and adequacy of the eligibility criteria.

A database will be created that is HIPAA compliant to store the information to perform analyses. A unique study number will be assigned to each patient that will be used for all analyses. Variables will be defined as described in section 11. The results of analyses will be described but no formal statistical analysis will be performed.

Grade ≥4 RT-related toxicities will be recorded in database and are described as in section 5.2. The ultimate allocation of a toxicity as RT-related or non-RT-related will be decided by the study committee. Toxicities of interest that occur within the 3-12 month time frame after RT start will be documented and analyzed using descriptive statistics.

The durations of treated lesion control, organ-specific control, distant metastasis free survival, progression-free, overall and cause specific survival as defined in section 11.1.5 will be calculated for each patient. Descriptive statistics will be used to estimate these secondary endpoints using the Kaplan-Meier method (secondary aims 1.2.1, 1.2.3).

The radiotherapy doses for each treated site will be recorded. The doses to the

corresponding normal tissues will also be recorded. The maximum dose to each site while staying within dose constraints will be described. The dose to each lesion will also be compared to the local control of the corresponding lesion and described.

13. CONFIDENTIALITY

13.1 Patient Confidentiality Issues

Study records that identify patients will be kept confidential. Study records will contain patients' name, address, and medical history number and will be available to the study doctor, research nurse, and data coordinator. Data collected in this study will be maintained on a password protected computer that only the primary investigator, co-investigators, research nurse, and data coordinator will be able to access. Study records will be secured in locked offices in the Department of Radiation and Cellular Oncology. Neither patient's name nor other personally identifying information will be used in any publication resulting from the research study.

14. BLOOD BANKING FOR FUTURE RESEARCH

14.1 Collection of blood

Biomarkers that have prognostic or predictive value are of great interest in the setting of managing patients with oligometastatic disease. Currently, the selection of patients for locally aggressive treatment to metastatic disease is based on clinical factors, such as tumor characteristics, interval to metastatic progression, burden of metastatic disease, and patient age or health. Circulating cell-free DNA is one such potential biomarker that can help identify the best patients for this therapy, given that patients with renal cell carcinoma have a higher content of cell-free DNA compared to normal controls [70].

Blood samples for future research will be collected for patients who provide consent. Blood (5 mL) will be drawn at 4 points during the study. This blood draw will be performed at the same time as phlebotomy for routine care purposes at baseline (pre-treatment), 3, 6 and 12 months post -RT. The blood will be labeled with the date of collection, the patient's initials, and protocol number.

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APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.