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Study Title
A Pilot Study of Stereotactic Radiosurgical Hypophysectomy for Intractable Pain from Bone Metastases

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TITLE: A Pilot Study of Stereotactic Radiosurgical Hypophysectomy for Intractable Pain From Bone Metastases

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SCHEMA

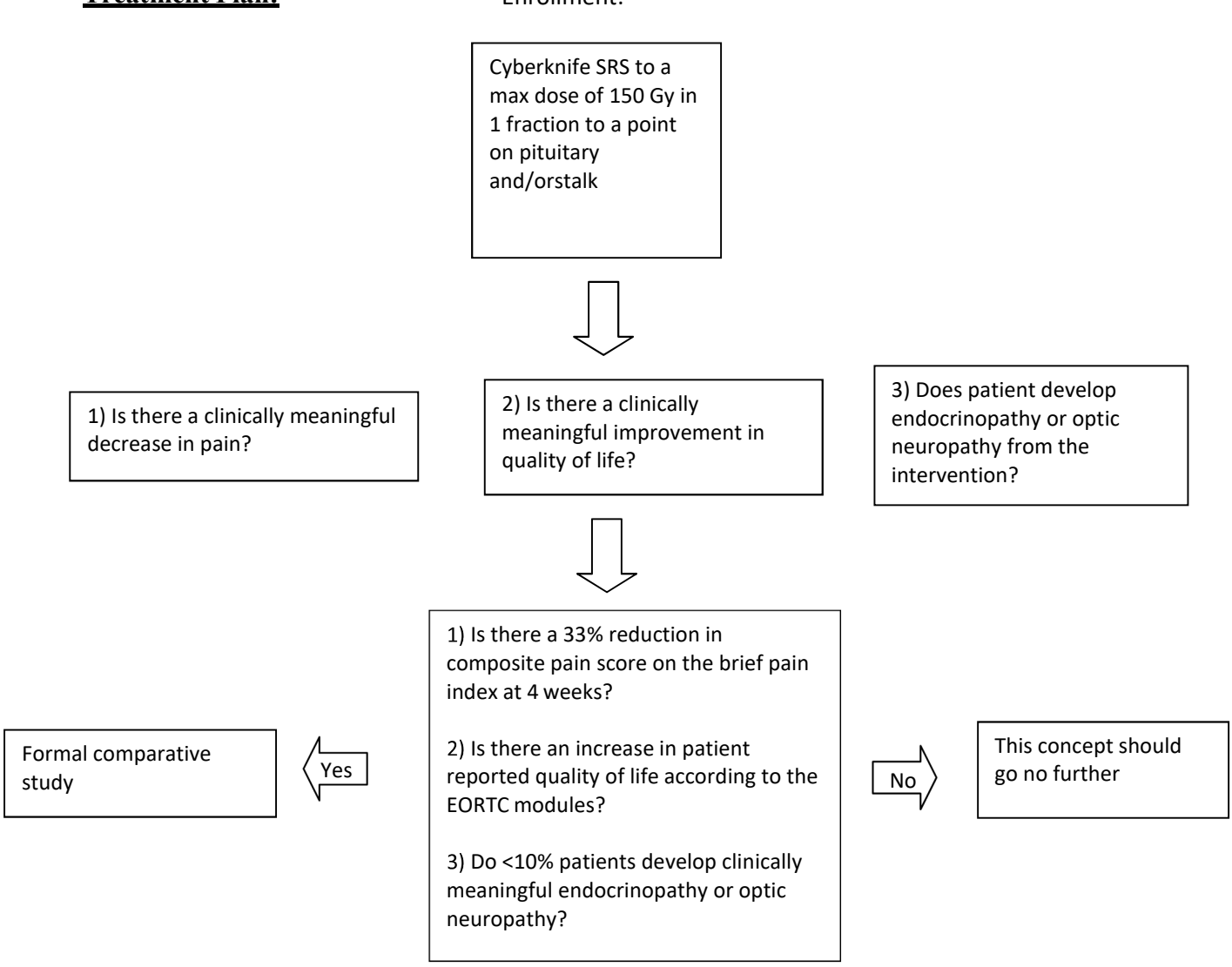
Major Eligibility Criteria:

1) Histologically proven malignancy
2) Radiographic evidence of bone metastases on CT, MRI, and/or bone scan
3) Intractable pain uncontrolled by medical management
4) Diffuse osseous pain not targetable by conventional radiation therapy
5) Progressive malignancy not amenable to curative management

Major Exclusion Criteria:

1) Focal pain amenable to focal radiation therapy or other focal therapies
2) Malignancies being managed with curative intent
3) Life expectancy <4 weeks
4) Prior radiation dose to the optic apparatus

Treatment Plan:



1. OBJECTIVES

1.1 Primary Objectives

To estimate the rate of clinically meaningful decrease in diffuse osseous pain (defined as 2 point reduction) following radiosurgical hypophysectomy at 4 weeks following completion of radiosurgical hypophysectomy

1.2 Secondary Objectives

1) To estimate the rate of clinically meaningful decrease in diffuse osseous pain following radiosurgical hypophysectomy at days 1-7, weeks 2 and 3, and monthly thereafter following completion of radiosurgical hypophysectomy

2) To estimate the rate of clinically meaningful increase in patient reported quality of life following radiosurgical hypophysectomy

3) To estimate the rate of reduction in opioid utilization following radiosurgical hypophysectomy

4) To estimate the rate of biochemical endocrinopathy following radiosurgical hypophysectomy

5) To estimate the risk of radiation induced optic neuropathy following radiosurgical hypophysectomy

6) To estimate the radiation-associated acute and long term neurologic toxicity of radiosurgical hypophysectomy

7) To estimate the rate of diabetes insipidus following radiosurgical hypophysectomy

8) To estimate the quality-adjusted survival of radiosurgical hypophysectomy

9) To estimate the relationship between pain response and cortisol levels

10) To estimate the rate of pain response in hormonally active and non-hormonally active tumors

11) To estimate the rate of pain response in morphine sensitive and morphine insensitive tumors

2. BACKGROUND AND RATIONALE

2.1 Prevalence and impact of cancer pain

Uncontrolled pain is common in cancer patients and adversely impacts their quality of life (1, 2). A recent meta-analysis suggests that more than half of cancer patients suffer from pain, irrespective of the stage of their disease (1). These rates are unfortunately even higher in patients with advanced, metastatic or terminal disease where almost two-thirds of patients (1) experience pain.

A survey of family members of cancer patients suggests disconnect between health care providers' assessment of pain management and that of patients and their families (3, 4), and numerous studies report global under-treatment of pain across cancer settings (5-14). Uncontrolled cancer pain poses a substantial burden, both economically, and in terms of patient's functional status, quality of life, and potentially overall survival (15-19). Pain also directly impacts sleep quality which is linked to psychological distress and a sense of hopelessness (20, 21).

2.2 Surgical and chemical hypophysectomy

Surgical hypophysectomy was first utilized in the management of cancer pain in the 1950s with the goal of neoplastic control through manipulation of endocrine function (22-27). It was hypothesized that pituitary hormones serve as mediators for cancer growth, especially for hormonally-active tumors, such as breast and prostate cancer. Although not academically rigorous studies, the authors reported marked oncologic responses as well as substantial improvement in osseous pain from metastatic disease. Interestingly, some investigations suggested improvement in pain following surgical hypophysectomy even in patients without a neoplastic response (28, 29).

Further investigations of the concept were conducted in the 1970s and 1980s with a primarily oncologic intent of tumor control of hormonally active tumors. Retrospective reviews patients treated with surgical hypophysectomy for hormonally mediated reported rates of tumor control ranging from 0-55% (30-32) following the intervention, with reduction in pain in 73-88% of patients (30-32).

Unexpectedly, reports of efficacy of transphenoidal hypophysectomy in reducing cancer pain of non-hormonally mediated tumors such as melanoma began to emerge in the 1980s (31). This reduction in pain occurred in the absence of tumor response but lasted 1-2 months (31).

Nonetheless, the approach was fraught with significant toxicities including diabetes insipidus, changes in mental status, cerebrospinal fluid leaks and meningitis (33). Concerningly, operative mortality rates were as high as 5.6% (33). In addition, it was not deemed appropriate in patients with an extensive disease burden or poor prognosis as their limited life expectancies did not warrant recovery from a large invasive surgery.

In the late 1970s and 1980s ethanol injections began to be utilized as a method of neuro-adenolysis. Complete pain relief, defined as improvement in pain allowing discontinuation of all pain medications, was achieved in 80-85% of patients, occurred

nearly immediately following the intervention and lasted for up to 2 years (33-35). Pain responses were more prevalent in patients with hormonally active tumors where they were reported in 94-95% (33, 36). Nonetheless, pain improved in 69% of non-hormonally active tumors as well (33).

Unfortunately toxicities of chemical pituitary neuro-adenolysis remained high and included diabetes insipidus, visual field deficits, and ophthalmoplegia (33, 35, 37). Therefore, while effective, the procedure should only be employed with caution and only in patients with a very poor life expectancy.

Interestingly, high rates of euphoria and hyperphagia have also been reported in treated patients, initially leading to a hypothesis that the hypothalamus may play an intermediary role (33, 36). However, an autopsy series revealed necrosis of the pituitary gland without histologic changes in hypothalamus, thalamus, brain stem, or pituitary stalk (34).

To date, the mechanism of the effect remains unknown. It has been hypothesized that the procedure might lead to increased secretion of endogenous opioids. However, naloxone administration does not reduce the pain response (36, 38). An increase in CSF endorphin levels has similarly been speculated (39), but this peak falls within hours in spite of a persistent pain response (40). One promising mediator may be the adeno-cortical system. This hypothesis is supported by a study of hormone and peptide levels in the CSF that demonstrated a rapid increase in ACTH at 24 hours following treatment in patients with complete pain relief, but not in patients with persistent pain (40). The levels remain elevated even 2 months following suggesting that it ACTH may play a central role.

2.3 Radiosurgical hypophysectomy

Given the toxicities associated with invasive surgical and chemical hypophysectomy, radiosurgical hypophysectomy has also been explored. An early study published in the 1970s suggested potential efficacy while avoiding the risks of anesthesia in critically ill patients, but did report toxicity including diabetes insipidus (41). Advances in the radiosurgical techniques including stereotactic approaches allowed the concept to be revisited thirty years later, with similar signals of efficacy but substantially reduced toxicity. Hayashi and colleagues performed a prospective study in which 9 patients with morphine sensitive pain were treated using stereotactic radiosurgery using Gamma Knife technology. They used an 8-mm collimator to deliver a maximum dose of 160 Gy to the interface of the pituitary gland and stalk. Specifically, the 50% isodose line was intended to cover at least 50% of the pituitary gland as well as the inferior aspect of the pituitary stalk. The absolute maximum point dose to the optic apparatus was limited to 8 Gy and the isocenter was moved until this constraint could be met. Remarkably, the authors report a 100% rate of complete pain relief that persisted for the duration of patient's life with a duration of follow-up ranging from 1 to 24 months). No patients experienced hypopituitarism, diabetes insipidus, visual disturbances or developed morphologic changes on follow-up MRI imaging.

Example case report and treatment plan

Although not rigorously studied academically, radiosurgical hypophysectomy has been performed by our group (WSR) using the Accuray CyberKnife system, demonstrating anecdotal evidence of both safety and efficacy. Figures 1 and 2 show an example treatment plan for an 80 year old man with widely metastatic prostate cancer taking greater than 500 mg morphine equivalent daily but with persistent 10/10 pain. He was treated with 150 Gy to a point on the pituitary gland/pituitary stalk in a single fraction. The patient demonstrated improvement in pain within 24 hours and over the subsequent 4 days his analgesia requirement reduced to approximately 200 mg morphine equivalent/day with 2/10 pain. Importantly, all normal tissue dose constraints are achieved, dramatically mitigating the risk of SRS induced injury.

Figure 1: Accuray CyberKnife SRS treatment plan. The green line represents the prescription isodose line

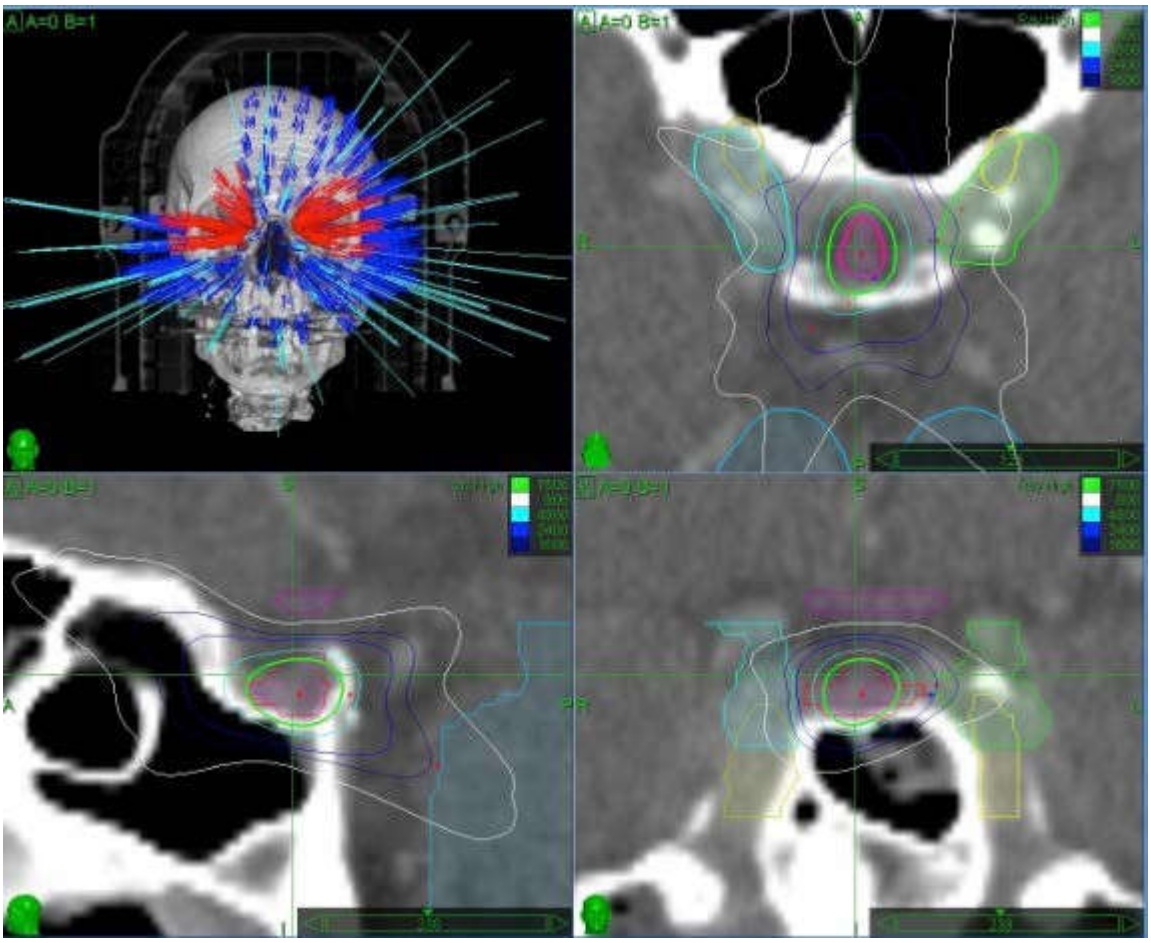
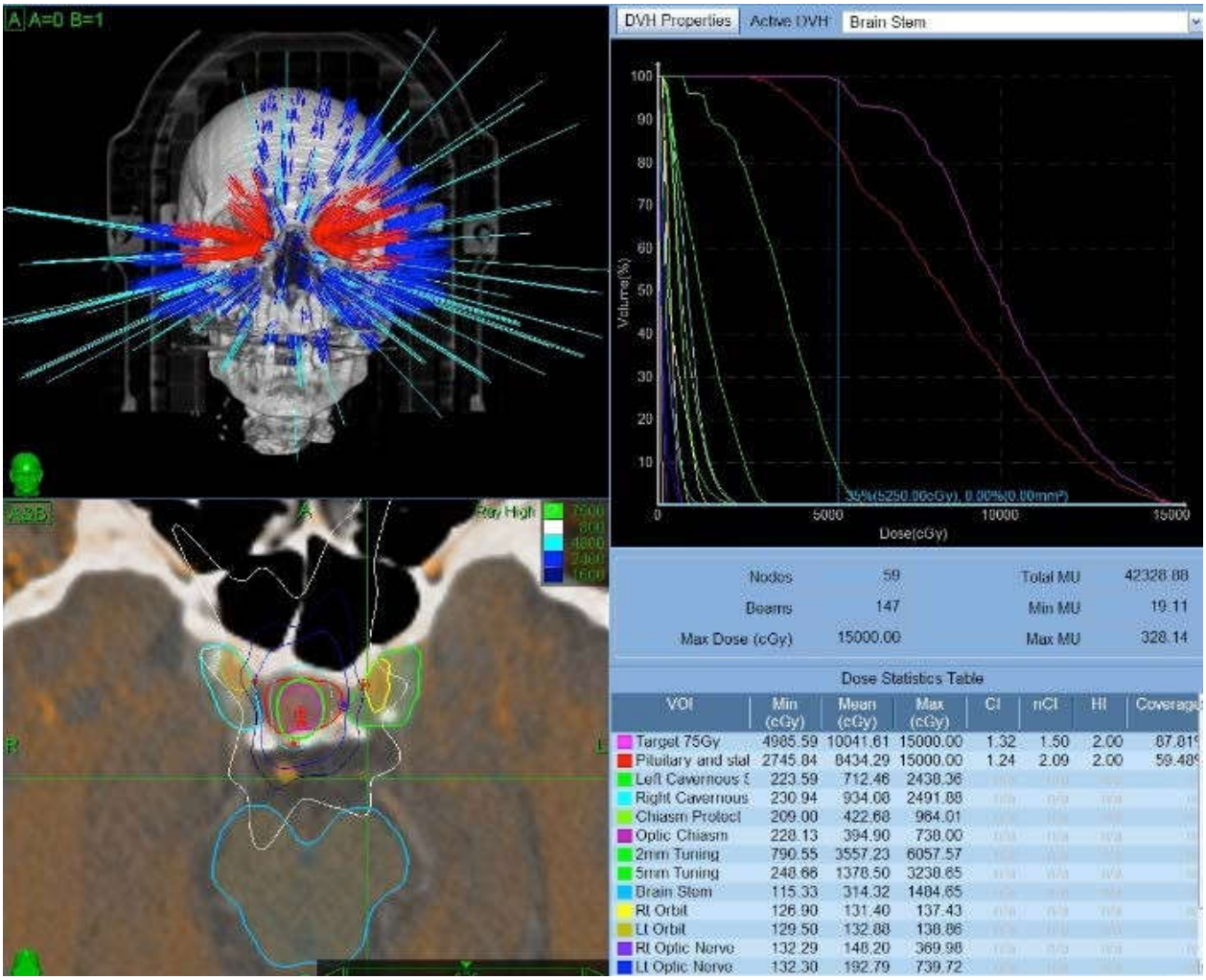


Figure 2: Accuray CyberKnife SRS treatment plan showing coverage of the intended target volume while meeting all normal tissue constraints.



In spite of the demonstrated feasibility and preliminary data suggestive of both safety and efficacy, radiosurgical hypophysectomy is underutilized in clinical practice, and many radiation oncologists are not even aware of its potential to reduce intractable cancer pain. This is likely because, to date, well-designed prospective studies have not been performed to further explore both the safety and efficacy of the intervention. This single arm pilot study is designed to fill that void. If successful, we plan to utilize the data to support the proposal of a larger scale follow-up clinical trial to a cooperative research group.

3. PATIENT SELECTION

3.1 Eligibility Criteria

1) Histologic proof or unequivocal cytologic proof of malignancy. This may be obtained from either the primary or any metastatic site

2) Radiographic evidence of bone metastases on plain x-ray, CT, MRI, and/or bone scan

3) Intractable pain uncontrolled by opioids, medical management, injections/ablation or surgical intervention that would be difficult to address with conventional radiation therapy or other standard options and is limiting the patient's function and quality of life. Intractable pain will be defined as a visual analogue score of at least 4 in spite of maximum tolerated doses of opioids and other medications.

4) Definitive radiographic progression of osseous and/or visceral metastases on standard staging scans (CT, MRI, bone scan, PET scan or any other standard of care imaging) performed within the last 3 months in spite of standard oncologic interventions and/or inability to tolerate standard oncologic interventions

5) Delivery of palliative chemotherapy or other systemic is permitted. However, no curative chemotherapy regimens are allowed

6) Life expectancy at least 4 weeks

7) Age≥ 18 years

8) Patients of childbearing potential (male or female) must practice adequate contraception due to possible harmful effects of radiation therapy on an unborn child

9) Patient must have the ability to understand and the willingness to sign a written informed consent document

10) All patients must be informed of the investigational nature of this study and must be given written informed consent in accordance with institutional and federal guidelines

3.2 Exclusion Criteria

1) Maximum cumulative BED3 to the optic apparatus including prior treatments and the current study treatment of >130 Gy.

2) Patients must not have a serious medical or psychiatric illness that would, in the opinion of the treating physician prevent informed consent or completion of protocol treatment

3) Isolated localized pain amenable to focal radiation therapy, or pain well controlled by opioids, medical management, injections/ablation or surgical intervention

4) Malignancies being managed with curative intent

5) Life expectancy <4 weeks

6) The tumor amenable to curative management

7) Chemotherapy delivery with curative intent

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 Registration Procedure

Prior to protocol enrollment and initiation of treatment, subjects must sign and date an IRB approved consent form. A centralized, 3-part registration procedure will be used. After eligibility screening and confirmation that a patient is eligible, patients who are selected to participate will be registered centrally at the SKCCC Johns Hopkins Lead Center, at the participating institution. The patient must give informed consent before beginning any study-specific procedures. Patient registration must be completed by the lead coordinating center before treatment is initiated. A complete, signed study consent and HIPAA consent are required for registration.

4.1.1 Registration at SKCCC, Johns Hopkins University. Confirm eligibility as defined in Section 3.

4.1.1.1 Obtain informed consent, by following procedures:

The investigator (or his/her designee) will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that he may withdraw from the study at any time, and that withdrawal of consent will not affect his subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The subject should read and consider the statement before signing and dating it, and will be given a copy of the document. No subject will enter the study or have study-specific procedures done before his informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

All subjects considered for enrollment in the study must complete an IRB-approved informed consent prior to any study-specific procedures being performed.
To register a patient, the participating site must contact the Lead Center's Study Coordinator about a potential candidate prior to sending documents. Once acknowledgement is made, the following documents must be completed and faxed to (443-287-8354) or e-mailed to the lead site:

- Signed patient consent form
- Eligibility checklist signed by the participating center PI
- Copies of all source documentation verifying eligibility criteria

The Lead Site will review the documents to confirm eligibility. To complete the registration process, the Lead Center will:

- Assign a patient study number
- Register the patient on the study with the Sidney Kimmel Comprehensive Cancer Center's Clinical Research Office.
- Fax or e-mail the unique patient study number and assigned study arm to the participating site.

Treatment must not commence until the patient has been registered with the Sidney Kimmel Comprehensive Cancer Center's Clinical Research Office.

5. TREATMENT PLAN

5.1 Radiation

5.1.1 Radiation Simulation and Prescription

Patients will be treated to a maximum point dose of approximately150 Gy in a single fraction. All patients will undergo CT simulation with 1 mm slices as well as MRI simulation including at least high resolution 1 mm slice T1 weighted MRI. They will be treated in a supine position using an aquaplast mask system for immobilization.

5.1.2 Target volume delineation

The PTV will be the same as the CTV (no expansion) and will include an approximately 8 mm region of the inferior pituitary stalk (~50% of the stalk) as well as at least 50% of the pituitary gland as visualized on axial and coronal T1 weighted post-gadolinium MRI. The target should be labelled as CTV_pituitary with capital letters, spacing and use of underscores applied exactly as indicated. The target contour may be modified during the planning process as necessary to meet the normal tissue constraint of the optic apparatus. All contours will be reviewed and approved by the treating radiation oncologist and a neurological surgeon. In addition, the principal investigator (KR) will review and approve all contours prior to initiation of treatment.

5.1.3 Definition of Critical Structures

All structures listed in the table below must be contoured and labeled. Capital letters, spacing and use of underscores must be applied exactly as indicated. All structures should be contoured on the planning CT, using the fused MRI for guidance as described below. Due to variance in eye position between the CT and MRI, the lenses and optic nerves should be contoured using the CT dataset only. All contours will be reviewed and approved by the treating radiation oncologist and a neurological surgeon. In addition, the principal investigator (KR) will review and approve all contours prior to initiation of treatment.

Standard Name	Description	Descriptive Details
Cavernous_Sinus_L	Left cavernous sinus	The left cavernous sinus will be delineated using the simulation CT and MRI as a reference.
Cavernous_Sinus_R	Right cavernous sinus	The right cavernous sinus will be delineated using the simulation CT and MRI as a reference
Lens_L	Left lens	Due to variance in eye position between the CT and MRI, if possible, the left lens should be contoured using the CT dataset only.
Lens_R	Right lens	Due to variance in eye position between the CT and MRI, if possible, the right lens should be contoured using the CT dataset only.
OpticNerve_L	Left optic nerve	Due to variance in eye position between the CT and MRI, if possible, the left optic nerve should be contoured using the CT dataset only.
OpticNerve_R	Right optic nerve	Due to variance in eye position between the CT and MRI, if possible, the right optic nerve should be contoured using the CT dataset only.
OpticChiasm	Optic chiasm	Located above the pituitary fossa, the optic chiasm includes both anterior and posterior limbs. It is best visualized on SPGR/MPR/TFE T1 MRI sequence, but should be confirmed on CT dataset due to potential variation in CT/MRI fusion.
Brainstem	Brainstem	The brainstem will be delineated using the simulation CT and MRI as a reference.

5.1.4 Compliance Criteria

The Per Protocol and Variation Acceptable categories are both considered acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is **required**.

NOTE: Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met.

Target Volume Constraints and Compliance Criteria

Name of Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable	Notes
CTV_pituitary	D_{min}(Gy)	>30 Gy	>25 Gy	Minimum dose to CTV_pituitary. However the minimum dose may be reduced if needed to meet normal tissue constraints
	$V75_{Gy}$ (%)	≥ 60%	≥ 50%	Volume receiving prescription dose of 75 Gy. However the coverage may be compromised further if needed to meet normal tissue constraints
	D_{max}(Gy)	150 Gy		The max point dose goal may be reduced if needed to meet normal tissue constraints

Normal Structure Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable	Notes
OpticNerve_L	D_{max}(Gy)	≤ 8 Gy	≤ 10 Gy	Maximum point dose to OpticNerve_L
OpticNerve_R	D_{max}(Gy)	≤ 8 Gy	≤ 10 Gy	Maximum point dose to OpticNerve_R
OpticChiasm	D_{max}(Gy)	≤ 8 Gy	≤ 10 Gy	Maximum point dose to OpticChiasm
Brainstem	D_{max}(Gy)	≤ 10 Gy	≤ 12 Gy	Maximum point dose to Brainstem
Cavernous_Sinus_L	D_{max}(Gy)	≤ 20 Gy	≤ 25 Gy	Maximum point dose to Cavernous_Sinus_L
Cavernous_Sinus_R	D_{max}(Gy)	≤ 20 Gy	≤ 25 Gy	Maximum point dose to Cavernous_Sinus_R

5.1.5 Dose Calculations

Primary dataset for dose calculation should be non-contrast treatment-planning CT scan of the entire head region using the smallest possible axial slice thickness not exceeding 2 mm.

5.1.6 Equipment, Radiation Technique, and Dosimetry

Patients will be treated using a megavoltage linear accelerator with nominal beam energy of 6 MV.

5.1.7 Risks of Radiation

Short term toxicities of radiation therapy include fatigue, alopecia, erythema or irritation of the skin, dry skin, headaches, worsening of current symptoms, edema of brain requiring steroids, ear pain or discomfort, damage to the baby if patient is or becomes pregnant, seizures, neurologic deficits depending on tumor location, edema of brain requiring surgery, death. Long-term toxicities include memory loss, hypopituitarism, carotid rupture, cranial nerve injury, brainstem injury, diabetes insipidus, cataracts, edema of the brain requiring steroids, vision loss, hearing loss, necrosis of brain requiring surgery second tumor or cancer caused by radiation.

5.2 Laboratory Analyses of Endocrine Function

5.2.1 Salivary cortisol will be collected pre-SRS, once anytime between days 1-7 post SRS, at week 4 following SRS, and then annually thereafter

5.2.2 Twenty-four hour urine volume will be collected pre-study, at 2 and 4 weeks following completion of SRS, at 3 months following completion of SRS and then annually therafter.

5.2.3 A pituitary laboratory panel including AM cortisol, free T4, TSH, IGF-1, prolactin will be collected pre-study, at 2 weeks, 4 weeks and 3 months following completion of SRS, and annually thereafter. We anticipate each of these blood draws to involve about 5 ml of blood.

5.3 Duration of Follow Up

Patients will be followed until the time of death or the time of data analysis.

5.4 Criteria for Removal from Study

Patients will be removed from the study for the following reasons:

5.4.1 Development of intercurrent, non-cancer related illness that prevents either continuation of therapy or regular follow-up.

5.4.2 The patient may decide to discontinue enrollment in the protocol at any time and for any reason.

All reasons for discontinuation of treatment must be documented.

6. STUDY CALENDAR

See Appendix A. Baseline evaluations are to be conducted within approximately 30 days prior to initiation of radiation therapy. Note that the study calendar is based on the ideal subject. The schedule should be followed as closely and realistically as possible, but may be modified due to problems such as scheduling delays, conflicts such as clinic closure or poor weather conditions, or other unforeseeable events. It is strongly preferred that the assessments be performed within 2 weeks of the outlined timeline. Surveys and pain scales may be completed by members of the clinical team, study team, or hospice team members.

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

7. MANAGEMENT OF TOXICITY

7.1 Acute Toxicity

Acute morbidity potentially associated with therapy will be monitored and recorded on the Radiation Oncology On-Treatment Evaluation Form for all patients from baseline to 90 days after completion of radiation therapy. Grading will be according to the RTOG Acute Morbidity Scoring Criteria as follows:

Organ	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Skin	No change over baseline	Faint erythema, epilation, dry desquamation, or decreased sweating	Tender or bright erythema, patchy moist desquamation, moderate erythema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Eye	No change over baseline	Mild conjunctivitis with or without scleral injection, increased tearing	Moderate conjunctivitis with or without keratitis requiring steroids and/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 over baseline.	Moderate external otitis requiring topical medication, serous otitis media, hypoacusis on testing only	Severe external otitis with discharge or moist desquamation, symptomatic hypoacusis, tinnitus, not drug related	Deafness
CNS	No change over baseline	Fully functional status with minor neurologic findings, no	Neurologic findings present sufficient to require home care. Nursing	Neurologic findings requiring hospitalization for initial management	Serious neurologic impairment which included paralysis, coma, or

		medications needed	care may be required. Medications including steroids and/or anti-seizure agents		seizures, despite medications. Hospitalization required

7.2 Late Toxicity

Late toxicity will be recorded on the Radiation Oncology Follow-up form at each follow-up visit greater than 90 days post completion of radiation therapy. Grading will be according to the RTOG Late Radiation Morbidity Scoring Schema as follows:

Organ	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Skin	None	Slight atrophy, pigmentation change, some hair loss	Patchy atrophy, moderate telangiectasia, total hair loss	Marked atrophy, gross telangioectasia	Ulceration	Death directly related to late radiation effect
Subcutaneous Tissue	None	Slight induration 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	
Spinal Cord	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurologic findings at or below cord level treated	Mono-, para-, quadra-plegia	
Brain	None	Mild headache, slight lethargy	Moderate headache, great lethargy	Severe headaches, severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures, paralysis, coma	

Eye	None	Asymptomatic cataract, minor corneal ulceration of keratitis	Symptomatic cataract, moderate corneal ulceration, minor retinopathy or glaucoma	Severe keratitis, severe, retinopathy or detachment, severe glaucoma	Panopthalmitis, blindness	

8. STATISTICAL CONSIDERATIONS

8.1 Study Design/Endpoints

8.1.1 Study Design

This is a single-arm pilot study of radiosurgical hypophysectomy for intractable pain from bone metastases

8.1.2 Primary Endpoint

A 2 point reduction in the worst pain severity score on the Brief Pain Index (ie: question number 3) at 4 weeks following completion of radiosurgical hypophysectomy compared to baseline will be considered as clinically meaningful decrease and recorded as a binary variable (yes/no) for each patient

8.1.3 Secondary Endpoints

1) A 2 point reduction in the worst pain severity score on the Brief Pain Index compared to baseline will be recorded as a binary variable (yes/no) for each patient at days 1-7, weeks 2 and 3, and monthly thereafter following completion of radiosurgical hypophysectomy . Patient reported pain according to the visual analogue scale will also be recorded at the same time points as well as at week 4.

2) Patient reported quality of life on the EORTC bone metastases, EORTC QLQ-C15-PAL , EORTC QLQ-BM22, EORTC QLC-30 and Euroqol EQ-5D modules will be recorded at weeks 1-4, and monthly thereafter following completion of radiosurgical hypophysectomy

3) Daily oral morphine equivalent dose compared to baseline will be recorded for each patient at weeks 1-4, and monthly thereafter following completion of radiosurgical hypophysectomy

   The following table will be used to convert all opiates to morphine oral dose equivalents (MOEDs), when applicable:

Morphine oral dose equivalents (APS)

Drug intake for prior 24 hours	Oral Equivalent	Parental equivalent	Doses and Total mgs taken	Conversion Factor	Total MOED (mg)
Morphine immediate release	30 mg	10 mg			
Morphine sustained release	30	10			
Codeine	200 mg	100 mg			
Oxycodone immediate release	20 mg	Not available			
Oxycodone extended release	20 mg	Not available			
Hydrocodone immediate release	30 mg	Not available			
Hydromorphone	7.5 mg	1.5 mg			
Methadone	10 mg	5 mg			
Fentanyl transdermal	1 mcg/hour equivalent to 2 mg oral morphine/hour				
TOTAL					

4) Menstrual history will be recorded and pituitary screening panel including AM cortisol, free T4, TSH, IGF-1, prolactin will be drawn at baseline, 2 weeks, 1 month and 3 months following completion of SRS and approximately annually thereafter

5) Development of radiation induced optic neuropathy will be recorded as a binary variable (yes/no) at weeks 1-4 and monthly thereafter. Patient reported assessment of visual acuity will be recorded at each time of these time points. Patients will be screened for changes in visual acuity using the Snellen Eye Chart at baseline and at any time point in which they clinically report a change. Patients with visual changes according to the Snellen Eye Chart will be referred for formal neuro-ophthalmologic evaluation

6) Use the RTOG/EORTC acute and late radiation morbidity scoring criteria at weeks 1-4 and monthly thereafter to record the radiation-associated neurologic toxicity of radiosurgical hypophysectomy

7) 24 hour urine volume will be checked at baseline, 2 weeks, 1 month, 3 months, and annually thereafter

8) Euroqol EQ-5D module will be recorded at weeks 1-4, and monthly thereafter following completion of radiosurgical hypophysectomy

9) Salivary cortisol levels will be collected pre-SRS, once anytime between days 1-7 post SRS, at week 4 following SRS, and then annually thereafter.

10) Primary histology will be recorded as either hormonally active or hormonally inactive

11) Baseline (pre-treatment) decrease in pain according to the visual analogue scale will be recorded for each patient. A 2 point decrease

following opiate administration will be defined as opioid responsive tumors.

8.2 Sample Size/Accrual Rate

8.2.1 Sample Size

We determine a sample size of 16 analyzable patients provides an appropriate level of estimation accuracy for the first study in the patient populations. A 2 point reduction in the worst pain severity score on the brief pain index at 4 weeks following completion of radiosurgical hypophysectomy compared to baseline will be considered as clinically meaningful decrease (CMD) and recorded as a binary variable for each patient. The following table summarizes the exact 90% confidence intervals when the observed proportions of CMD at 4 weeks are 25% - 75% with 16 analyzable cases. For example, when the proportion of CMD is 50%, a sample size of 16 analyzable cases will provide a two-sided 90% confidence interval [27.8%, 72.1%]. Guarding against a 20% of ineligible and drop-out rate prior to week 4 (progression, death, etc.), the final sample size is 20 patients. If a higher rate of ineligible and drop-out rate is observed, subjects may be replaced to allow for at least 16 analyzable cases observed. A promising treatment effect warranting further evaluation would be at least 4 of 16 analyzable patients having an improvement in the primary endpoint measure.

Observed number and proportion of patients experienced CMD	90% exact confidence interval	
	Lower (%)	Upper (%)
4 (25%)	9.1	48.4
6 (37.5%)	17.8	60.9
8 (50%)	27.8	72.1
10 (62.5%)	39.1	82.2
12 (75%)	51.6	90.9

8.2.2 Accrual

We anticipate enrollment of approximately 1 patient per month to the protocol with accrual completed in approximately 2 years. Given that Johns Hopkins is a large referral center, there are a high volume of patients with metastatic cancer tumor patients treated across our system, as well as an established recruitment infrastructure within the Johns Hopkins cancer centers.

8.3 Stratification Factors

There will be no stratification factors upon initial enrollment in the protocol.

8.4 Statistical Analysis Plan

All analyses performed in this study are exploratory in nature, and intended for

hypothesis generation only. The definitions of each endpoint, as well as the timepoints of interest, are elaborated in section 8.1.2 and 8.1.3. Assessments of Brief Pain Index, various patient reported outcome (e.g., EORTC tools) and other secondary endpoints at baseline and each subsequent assessment, as well as their change from baseline will be summarized using descriptive statistics. The summary at baseline and at each time point is based on all analyzable subjects with a measurement at respective time point. The change from baseline analysis will only include subjects who have an assessment at baseline and at the subsequent time point. For binary outcomes, the associated Clopper-Pearson 90% confidence interval of rates of decrease will be calculated. For continuous outcomes, their measurements at baseline and subsequent time points will be also compared using the pair t-test or Wilcoxon signed-rank test if the parametric assumptions are not met. Effect size of changes in continuous outcomes at different time points will be calculated based on Cohen's d. Longitudinal data analysis may also be performed to characterize the trend of repeated measurements over time using hierarchical formulation of the linear mixed model.

EQ-5D consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The EQ VAS records the subject's self-rated health state on a 100-point vertical, visual analogue scale (0 = worst imaginable health state; 100 = best imaginable health state. Subjects' overall health state on a visual analog scale (EQ-VAS) at each assessment time point will be summarized using descriptive statistics. Proportion of subjects reporting problems for the five EQ-5D dimensions at each assessment time point will be summarized by level of problem. Percentages will be based on number subjects assessed at assessment time point. Quality-adjusted survival can be defined by the weighted sum of different time episodes added up to a total quality-adjusted life-year [U= sum of quality (qi) of health states K times the duration spent in each health state] (Glasziou 1990). Glasziou's multiple health-state (Q-TwiST) models will be used based on the repeated measures of 5-item utility score EQ-5D.

As collection of cortisol levels will be coincide with the collection of pain index, the correlation between cortisol change and pain response from baseline to each subsequent timepoint will be computed using Spearman's rank correlation coefficient.

8.5 Safety Monitoring

All adverse events will be reported according to the CTCAE v4 criteria. Given that this is a pilot study with a small sample size that we anticipate will accrue over a 1.5-2 year period, there is no formal stopping rule. However, adverse events will be reviewed on an ongoing basis and reported to the IRB and data safety monitoring committee when appropriate.

Safety will be monitored through the rate of all treated patients that develop clinically meaningful endocrinopathy or optic neuropathy as a result of the protocol SRS. A Bayesian safety monitoring rule will be used to evaluate the rate of adverse events of

interest every other patient, and accrual will be suspended at any time if there is sufficient evidence of excessive toxicity. Specifically, the Bayesian toxicity monitoring rule suspends accrual anytime if the posterior probability of adverse event of interest being larger than 10%, is 70% or higher, using a Beta prior of (0.1,4.9). Such monitoring rule corresponds to the following accrual stopping criteria 1) when the number of evaluable patients is less than 8, stop accrual once observing 2 AEs; 2) when the number of evaluable patients is more than or equal to 8, stop accrual once observing 3 AE. The following table summarizes the operating characteristics of the stopping rule.

Underlying toxicity	0.05	0.1	0.15	0.2
% of time study stops	5.7%	26%	47.6%	67.9%
Expected sample size	15.6	14.3	12.7	11.1

9. ADVERSE EVENTS AND RECORDING

9.1 Definition of Adverse Event (AE)

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition during or following an exposure to a treatment, whether or not considered causally related to the treatment. An undesirable medical condition may be symptoms (headache, nausea), signs (tachycardia, enlarged liver), or abnormal results of an investigation (MRI, laboratory finding). In clinical trials, from the time of signing an informed consent, an AE may include an undesirable medical condition, occurring at any time, even if no trial treatment has been administered.

9.2 Radiation Related Adverse Events

All radiation related adverse events will be recorded on the local toxicity case report forms or in Mosaic.

10. SERIOUS ADVERSE EVENTS (SAE) AND REPORTING

10.1 Serious Adverse Event

10.1.1 Definition of Serious Adverse Event

A serious adverse event is an AE occurring at any point during a clinical trial that fulfills one or more of the following criteria:

- Results in death.
- Is immediately life threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Is a congenital abnormality or birth defect.
- Unexpected event that cause harm or place person at a greater risk of harm

than was previously known or recognized, and which was possibly related to the research. Unexpected means that the event was not described in the consent form or the event exceeded the expected severity.

- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

10.2 SAE Reporting Guidelines for Johns Hopkins Hospital

All SAE, with the exception of death, must be reported to the Johns Hopkins Hospital Institutional Review Board (JH-IRB) within 10 working days of the principal investigator learning of the event. Reporting for the death of a patient which was unexpected (i.e.: not related to a risk of participation that was listed in the protocol or the consent document, and was more likely than not to be caused by the research procedure/intervention, must be reported to the JH-IRB within 3 working days of when the principal investigator receives the report of the death. Reporting for death of a participant that was expected due to the nature of the patient's underlying disease or condition, or identified as caused by a possible risk of the study procedure/intervention as described in this protocol or consent form, must be reported to the JH-IRB within 10 working days from the time the principal investigator learns of the event. If death occurs 30 days after the participant has stopped or completed their study treatment, the principal investigator does not have to report the death until the time of continuing review.

11. DATA AND SAFETY REPORTING/ REGULATORY CONSIDERATIONS

11.1 Data Quality Monitoring

The PI shall internally monitor the progress of the trial, including review and confirmation of all safety/treatment-related outcomes, response assessments, safety reports and/or any related source documentation. PI shall also establish additional external data/safety monitoring oversight (MEC, DSMB, etc), as required or detailed in protocol.

11.2 Data Safety Monitoring

All SAE's and major protocol deviations that occur at Johns Hopkins Hospital will be submitted to the Sidney Kimmel Comprehensive Cancer Center Data Monitoring Committee for review per Institutional guidelines. In addition, the overall study safety and potential activation of the study's early stopping rules will be assessed at the time of every SAE. The Sidney Kimmel Comprehensive Cancer Center Data Monitoring Committee will serve as the DSMC for this study.

11.3 Data Reporting

11.3.1 Method

Data will be collected on Case Report Forms (CRF's). These CRF's will be completed by the Study Coordinator. The CRF's for each subject will be kept in a separate research binder. Along with each completed CRF there will be corresponding source documentation filed for verification. The Principal Investigator, Research Nurse, and Study Coordinator will informally meet on a regular basis to make sure that the trial is progressing as mandated by the

protocol. The Clinical Research Office (CRO) will audit this trial per their standards to ensure and verify that the protocol is being carried out according to plan as well as to verify that data included on subject CRF's are accurate. Exit reports generated as a result of these CRO audits will be forwarded to both the Safety Monitoring Committee as well as to the IRB of record for review.

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Appendix A: Study Calendar

	Pre-Study[1]	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Wk 2	Wk 3	Wk 4	Mo 2	Mo 3	Mo 4	Mo 5	Mo 6	Monthly	Annually
Informed consent	x																	
Demographics	x																	
Medical history[2]	x																	
Physical exam	x																	
Vital signs	x																	
Performance status	x																	
Brief Pain Index[3]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Visual Analogue Pain Scale[3]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
EORTC QOL surveys[3,4]	x							x	x	x	x	x	x	x	x	x	x	
Daily Oral Morphine Equivalent Dose[3]	x							x	x	x	x	x	x	x	x	x	x	
Pituitary Laboratory panel[5,6]	x								x		x		x					x
Snellen Visual Acuity Chart[7]	x																	
Patient reported visual acuity[3,7]	x							x	x	x	x	x	x	x	x	x	x	
NCI Common Toxicity Criteria[3]																		
RTOG Acute/Late Morbidity Criteria[8]								x	x	x	x	x	x	x	x	x	x	
24 hour urine volume[6,9]	x								x		x		x					x
Salivary cortisol[6]	x	X[10]									x							x

[1] Baseline evaluations are to be conducted within 4 weeks prior to start of protocol therapy.
[2]Medical history should be a complete history at pre-study evaluation, but later histories may be interval toxicity evaluations only.
[3]Pain, quality of life, and toxicity surveys may be conducted in person or over the phone. Reports from visiting hospice nursing staff may be utilized if appropriate
[4]EORTC QOL surveys include EORTC bone metastases, EORTC QLQ-C15-PAL , EORTC QLQ-BM22, EORTC QLC-30 and Euroqol EQ-5D modules
[5]Pituitary screening consists of a menstrual history, AM cortisol, free T4, TSH, IGF-1, prolactin
[6]Laboratory studies and 24 hour urine volume will be performed approximately according to the schedule outlined above. However, studies which are delayed or missed as a result of the deterioration of the patient's clinical condition, other adversity, or logistical challenges will not be considered protocol violations. To better coordinate research sample collection with routine lab draws, modifications to the sample collection timeline are allowed and will not be considered protocol deviations.
[7] Patients who report a change in their vision will undergo additional screening for visual acuity according to the Snellen Eye Chart. All patients will complete this evaluation at baseline
[8]Use RTOG Acute Toxicity Criteria during RT and for first 6 months following completion of RT. Use RTOG Late Toxicity Criteria at baseline and at scheduled intervals 6 months following completion of RT.
[9]24-hour urine volume will be collected to screen for diabetes insipidus
[10] Salivary Cortisol can be completed anytime from Day 1 to Day 7.