**Interstitial Radioactive Iodine Implants for the Treatment of Pan-invasive Pituitary Macroadenomas**

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## INDEX

## STUDY SYNOPSIS

### Interstitial Radioactive Iodine Implants for the Treatment of Pituitary Macroadenomas

Schema

**Patient Population**: (See Section 3.0 for Eligibility)
Patients must have biopsy proven pan-invasive pituitary macroadenomas of the pituitary gland. Pan-invasive for the purposes of the protocol will be defined as meeting each of the following 2 major criteria:

1. tumor volume greater than 20 cc at enrollment, and
2. suprasellar extension.

In addition, a pan-invasive tumor must meet any one of the following 3 minor criteria:
a) unresectable tumor invasion into a cavernous sinus,
b) bone or bone marrow invasion into the clivus or temporal bones, or
c) tumor extension in any direction unlikely to be completely removed specifically by a transphenoidal surgical approach.

Patients who meet the two major criteria above (1 and 2) and are medically inoperable for tumor resection (due to confounding co-existing medical problems) are eligible without meeting any of the three minor criteria (a, b, or c).

Patients should be immediately threatened for vision loss or other significant neurological impairment directly related to tumor mass effect. As such, all patients enrolled would likely benefit from tumor response (shrinkage).

Patients with pituitary carcinomas are not eligible.

Number of patients = up to 12 in each or two cohorts listed below (total up to 24).

Patients will be divided into two cohorts depending on if they have been previously treated with radiotherapy or not.

Eligible patents may have a functioning or non-functioning adenoma and may have previously undergone a surgical resection for their adenoma.

The goal of the study is primarily to monitor for tumor shrinkage after seed implantation. Additional outcomes that will be monitored are change in visual fields, potential toxicities (acute and late) related to the treatment, progression free survival, and changes in patient reported outcomes.

**ELIGIBILITY CHECKLIST**

**Case #** _____ (page 1 of 3)

_____(Y) 1. Does the patient have a pathologically confirmed pituitary adenoma?

_____(Y) 2. Is the patient's tumor causing an immediate threat to vision or other significant neurological problems due to tumor mass effect?

_____(Y) 3. Is the tumor grossly visible on MRI or CT?

_____(Y) 4. Is the tumor volume >20cc?

_____(Y) 5. Is there suprasellar extension of the adenoma (extension above the diaphragma sellae)?

_____(Y) 6. Does the tumor extension meet any one of the following 4 criteria?
_____(Y/N) 6a. Is there unresectable tumor invasion into a cavernous sinus?
_____(Y/N) 6b. Is there bone or bone marrow invasion into the clivus or temporal bones?
_____(Y/N) 6c. Is there tumor extension in any direction unlikely to be completely removed by specifically a transphenoidal surgical approach?
_____(Y/N) 6d. The responses to 6a, 6b, and 6c are all NO; however, the patient is medically inoperable for tumor resection due to confounding co-existing medical problems?

_____(Y/N) 7. Has the patient previously been treated with radiotherapy to either the central skull base or central brain?

_____(Y) 8. Has the patient been medically cleared to receive general anesthesia and stereotactic seed placement?

_____(Y/NA) 9. If female, was there a negative serum or urine pregnancy test performed within 72 hours prior to treatment for women of childbearing potential?

_____(N) 10. Does the patient's pituitary tumor histology reveal carcinoma?

_____(Y) 11. Did the patient provide study-specific informed consent prior to any protocol-specified procedure(s)?

_____(N) 12. Does the patient have serum creatinine > 1.2 mg/dl or a history of severe renal dysfunction?

_____(N) 13. Does the patient have uncontrolled allergy to MRI contrast dye?

_____(N) 14. Does the patient have a contraindication to MRI such as iron containing particles in the body (e.g. iron shavings in the eye), surgical implants (e.g. aneurysm clip), or implanted electronic device (e.g. pacemaker)?

_____(Y/N) 15. Is the patient's pituitary adenoma hormonally functional?

_____(Y/N) 16. Has the patient had a previous surgery for resection of pituitary adenoma?
_____(#) If yes, how many previous surgeries?

**(Continued on next page)**

**ELIGIBILITY CHECKLIST** (page 2 of 3)

**The following questions will be asked at Study Registration:**

_____ 1. Name of institutional person registering this case?

_____(Y) 2. Has the Eligibility Checklist (above) been completed?

_____(Y) 3. Is the patient eligible for this study?

_____ 4. Date the study-specific Consent Form was signed? (must be prior to study entry)

_____ 5. Patient's Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]

_____ 6. Verifying Physician

_____ 7. Patient's ID Number

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)

_____ 11. Gender

_____ 12. Patient's Country of Residence

_____ 13. Zip Code (U.S. Residents)

_____ 14. Patient's Insurance Status

_____ 15. Will any component of the patient's care be given at a military or VA facility?

_____ 16. Calendar Base Date

_____ 17. Registration/randomization date: This date will be populated automatically.

**(Continued on the next page)**

**ELIGIBILITY CHECKLIST**

**Case #** _____ (page 3 of 3)

_____(Y/N) 18. Tissue/Urine/Blood kept for cancer research?

_____(Y/N) 19. Tissue/Urine/Blood kept for medical research?

_____(Y/N) 20. Allow contact for future research?

Completed by _____ Date _____

Investigator Signature _____ Date _____

## INTRODUCTION

### 1.1 Epidemiology

1.1.1 Pituitary adenomas constitute 10-20% of all central nervous system tumors.[1,2] Patients with secretory adenomas most frequently present with endocrinopathies; the goal of therapy in these cases is normalizing the endocrinopathy and eliminating further lesion growth. First-line therapy can be either medical or surgical depending on the hormone being secreted.[3] Thirty percent of pituitary adenomas are nonsecretory and present clinically due to their progressive increase in size and the mass effect exerted on the surrounding tissues, most commonly, the optic apparatus.[4] Controlling tumor growth and preserving vision are the most important factors in the treatment of nonsecreting adenomas. Surgery is considered first-line treatment for these tumors.

Tumors with their greatest diameter of less than 10mm are classified as “microadenoma”, whereas those with a diameter of 10mm or more are considered “macroadenomas”.[5] Due to their benign nature and variable clinical presentation, pituitary adenomas may become very large, a factor that complicates treatment. Widespread surgical and radiologic interest in these tumors has resulted in various definitions of pan-invasive or “giant” pituitary adenomas. Both Fisher et al.[6] and Symon et al.[7] defined giant adenomas as those showing suprasellar extension of more than 40 mm in any direction from the midline of the jugum sphenoidale. Symon et al. also considered giant adenomas to be tumors extending within 6 mm of the foramen of Monro. Others considered adenomas with suprasellar extension of Hardy grades C and D as being large or giant.[8] Mohr et al. felt that having a superior margin more than 20 mm above the jugum sphenoidale was the key to identifying giant adenomas.[9] More recently, Goel et al. defined giant adenomas as those with greater than 4 cm in maximum diameter, further subclassifying them into four grades according to invasion and patterns of extension.[10] Despite definitional variations, all of the authors agree that very large tumors are difficult to treat by surgery alone and that adjuvant therapy is necessary.

### 1.2 Standard therapy

1.2.1 Giant or pan-invasive pituitary adenomas are a surgically challenging subset of sellar tumors. Although both the transsphenoidal and transcranial approaches have been used to remove giant adenomas, the transsphenoidal approach is generally favored because of decreased morbidity and a more direct trajectory to the long axis of the tumor. In most series of giant pituitary adenomas, the transsphenoidal approach has been the predominantly utilized operation.[9-13] A significant drawback of the standard transsphenoidal approach for giant adenomas is poor visualization of the suprasellar components.[14] The microscope lens and light source sit at the end of the long, narrow Hardy retractor, which limits the field of view. If the suprasellar extent of the tumor does not deliver itself into the surgeon's line of sight, then these aspects of the tumor are often unresected.[14] One option is to perform multiple staged surgeries. The staged transsphenoidal method or open sella method was proposed by Saito et al.[15] After an initial transsphenoidal operation, a second transsphenoidal procedure is performed in a delayed fashion with the expectation that residual suprasellar tumor may descend into the sella facilitating re-resection. In the series by Mortini et al.[11], the majority of patients that required staged procedures underwent a transsphenoidal operation followed by a transcranial procedure. Alleyne et al.[16] described their experience with a combined simultaneous transsphenoidal and transcranial approach. The gross total resection rate of 40% in the smaller series of Alleyne et al.[16] compares favorably with the experience of larger series of giant adenomas, which have gross total resection rates of 14.7-29.65%. In addition, more advanced surgical techniques have been described to better obtain a complete resection of macroadenomas. Added exposure provided by a Le Fort I maxillotomy has shown to facilitate a total or near total (>95%) resection of macroadenomas that have been incompletely resected by a traditional transnasal, transspenoidal approach.[17]

The clinical course and surgical outcome in cases with giant pituitary adenomas have generally been reported to be poor.[8,9,18-20] Treatment of pituitary adenoma with subtotal resection alone is associated with a risk of recurrence that approaches up to 80%.[21,22] Radiotherapy is commonly

used in cases of tumor recurrence[23] or may be used prophylactically after resection if there is evidence of residual tumor on postoperative neuroimaging. Long-term control of pituitary adenomas after transsphenoidal resection varies from 50 to 80%.[1,2,24-27]

In the past, conventional fractionated radiotherapy was the most common form of radiation therapy for pituitary adenomas. A review done by Minniti et al.[28] compared 10 studies from 1989 to 2000 on conventional radiotherapy for non-secretory adenomas. This review demonstrated an overall progression-free survival in the region of 80–90% at 10 years and 75–90% at 20 years. Therefore, conventional radiotherapy does offer very good local control rates. More recently, stereotactic techniques have been used that allow a more precise delivery of a higher dose of radiation to the target in either a single dose as SRS, or in multiple doses as fractionated SRT. These techniques use gamma radiation (with the Gamma Knife), a modified linear accelerator, or proton beams. Minniti et al.[29] reviewed 13 studies of SRS for non-secretory adenomas, and reported a tumor growth control rate of 87–100% with a follow-up of 6–60 months, in line with the results seen for conventional fractionated radiotherapy. However, a limitation of using SRS is that the adenoma must be small in volume and not be within 3 mm of the optic pathways.

## 1.3 Deficiencies with standard therapy

1.3.1 As mentioned above, for patients' who present with worsening symptoms secondary to mass effect on the surrounding tissues (deterioration of visual fields, headaches, loss of consciousness), surgical resection should be the primary intervention. However, depending on the size and infiltration of the adenoma, achieving a complete total resection can be difficult, therefore leading to an increased rate of recurrence. Extensive surgical procedures used to obtain radical removal of large pituitary adenomas, particularly by transcranial approaches, have been associated with brain, optic nerve, or vascular injuries, or panhypopituitarism resulting in increased surgical morbidity and mortality.[15,30,31] A higher rate of complete resection and fewer optic and other cranial nerve complications are associated with the transphenoidal approach. Still, in some patients the tumor cannot be removed or surgery may be associated with untoward toxicity.

Additionally, some patients are not candidates for surgical intervention due to the presence of certain co-morbidities. For these patients, treatment with conventional fractionated radiotherapy is a potential option. Radiotherapy alone has been shown to improve visual symptoms if visual field impairment was initially mild.[32-36] However, these effects are not usually appreciated until up to 2 to 3 years following treatment. For both surgical resection and conventional radiotherapy, the extent of the visual function recovery mainly depends on the preoperative deficits.[37]

## 1.4 Rationale and preliminary evidence for protocol therapy

1.4.1 Given the need to treat patients with pan-invasive macroadenomas that were experiencing worsening symptoms secondary to mass effect on surrounding tissues and who have previously underwent surgical resection with recurrence of disease or who were not candidates for surgical intervention, an alternative intervention was sought to decompress the adenoma and prevent further deteriorating symptoms or to possibly improve their symptoms.

Previous experience in the treatment of meningiomas with brachytherapy using permanent interstitial implantation of high activity iodine-125 (I-125) seeds provided the impetus for this current protocol. Kumar et al.[38-40] treated 13 patients with interstitial high activity I-125 seeds. Indications for implantation included recurrence after initial surgery or as a primary modality of treatment in patient who were not candidates for surgery. All 13 patients were alive at a median follow up of 25 months. Nine of the 13 patients achieved complete resolution of the tumor, while in the remaining four, more than 50% reduction in tumor volume was noted. The striking finding of this study was the time-frame in which tumor response was observed. The minimum time to achieve complete response was 3 months.[39,40] Additionally, no acute or late complications secondary to this technique of brachytherapy was observed. Given these promising results, we

sought to apply a similar technique for the treatment of pan-invasive pituitary macroadenomas that required rapid decompression in order to prevent further deterioration of symptoms.

There are several advantages in utilizing this technique for the treatment of pituitary adenomas. Tumors in the central nervous system are in close proximity to cranial nerves, cerebral blood vessels, and the brain stem. A tight dosimetry is of vital importance while treating tumors in this region. I-125, because of its low gamma energy, produces a steep dose gradient permitting delivery of a high tumor dose with a low dose to adjacent structures.[41] By using I-125 brachytherapy, the dose distribution can be tailored to fit the tumor shape by selecting seed placement at desired locations. The seeds are placed under stereotactic procedures which can be verified with imaging, making the treatment more accurate. Additionally, the dose rate is a key determinant of the biological effect of a given dose of radiation such that as the dose rate is lowered the biological effect is reduced and so are the side effects. This so called 'dose rate effect' is most pronounced in the range between 1 and 100 cGy/min and more so in normal vs. tumor tissue.[42] This partially accounts for the relative normal tissue sparing with brachytherapy, which confers an increased therapeutic ratio for this treatment. The dose rate effect is explained by the ongoing repair of sublethal radiation damage during low-dose rate exposures and the fact that this repair is more efficient in normal tissue. Also, the neoplastic cells in a solid tumor tend to be asynchronously scattered in all phases of the cell cycle, and under continuous low-dose rate irradiation, they tend to synchronize to the radiosensitive G2 and M phases.[43] The radiation dose rate effect should have a profound effect on the therapeutic ratio of brachytherapy applications for brain tumors if, in fact, there is efficient repair of sublethal damage in the brain.[44] The dose rate in the Kumar et al. study[39,40] was 5 cGy to 25 cGy per hour and given that no acute or late complications were noted in their study, proposes that this treatment modality is well tolerated.

Interstitial irradiation of pituitary adenomas has been described before. One of the first studies exploring the role of interstitial irradiation in the treatment of pituitary adenomas was published in 1960 by Ramsay.[45] These initial attempts with the implantation of radioactive gold and yttrium seeds unfortunately had a high incidence of complications. However, significant advances in localization and guidance have occurred since then. More current studies have shown favorable outcomes. Kumar et al.[46] presented a case-report of one patient experiencing correction of bilateral blindness secondary to a recurrent pituitary adenoma with the implantation of a single high-activity iodine-125 seed.

## 1.5 Description of protocol therapy

1.5.1 This study is a single arm Phase II pilot trial. Patients enrolled on the trial will undergo implantation of high activity iodine-125 seeds into their pituitary adenoma as outlined in sections 6 and 7. The tumor response to treatment will be monitored as well as change in visual fields, associated adverse effects, progression free survival and patient reported outcomes.

## 1.6 Who would benefit from protocol therapy?

1.6.1 Patients that would be expected to benefit from protocol therapy are those who are experiencing worsening neurological symptoms secondary to mass effect of their macroadenoma and who have previously undergone a surgical resection with recurrence of their disease or who are not candidates for surgical resection. These patients would be expected to benefit from decompression of their adenoma and given the findings seen in the treatment of meningiomas as stated above, we anticipate that implantation of interstitial high activity iodine-125 would lead to regression of their adenoma over the course of a few months, thereby preventing further deterioration of their symptoms and possibly even improvement in some cases.

## 2 OBJECTIVES

### 2.1 Primary objective

2.1.1 To determine if placement of interstitial radioactive iodine seeds for the treatment of pituitary macroadenomas can lead to a partial response (reduction in 30% of tumor volume) or greater response within 12 months from the implant procedure.

### 2.2 Secondary objectives

2.2.1 To determine if treatment results in a change of the patient's Humphrey visual field testing
2.2.1.1 Timeframe of assessment is up to 5 years post therapy

2.2.2 To assess for potential toxicities associated with interstitial seed placement
2.2.2.1 Specific toxicities that will be monitored are cerebrospinal fluid rhinorrhea, radiation-induced necrosis, changes in visual field deficits, changes in visual acuity, changes in auditory acuity, worsening headaches, and development of neurocognitive and/or short-term memory deficits
2.2.2.2 Timeframe of assessment is up to 5 years post therapy

2.2.3 To determine the progression free survival
2.2.3.1 Timeframe of assessment is up to 5 years post therapy

2.2.4 To determine the effect of the treatment on quality of life evaluations (patient reported outcomes)
2.2.4.1 Timeframe of assessment is up to 5 years post therapy

2.2.5 To evaluate the cost-utility of the treatment arm (in terms of the primary outcome) in comparison with other widely accepted cancer and non-cancer therapies
2.2.5.1 Timeframe of assessment is up to 5 years post therapy

## 3 PATIENT SELECTION

### 3.1 Inclusion Critera

3.1.1 Pathological or radiographic diagnosis of a pan-invasive pituitary macroadenoma

3.1.2 Pan-invasive for the purposes of the protocol will be defined as meeting each of the following 2 major criteria: 1. tumor volume greater than 20 cc at enrollment, and 2. suprasellar extension. In addition, a pan-invasive tumor must meet any one of the following 3 minor criteria, a) unresectable tumor invasion into a cavernous sinus, b) bone or bone marrow invasion into the clivus or temporal bones, or c) tumor extension in any direction unlikely to be completely removed by specifically a transphenoidal surgical approach.

3.1.3 Patients who meet the two major criteria above (1 and 2) and are medically inoperable for tumor resection (due to confounding co-existing medical problems) are eligible without meeting any of the three minor criteria (a, b, or c).

3.1.4 Patients should be immediately threatened for vision loss or other significant neurological impairment directly related to tumor mass effect. As such, all patients enrolled would likely benefit from tumor response (shrinkage).

3.1.5 Patients must have visible tumor on imaging studies (MRI or CT)

3.1.6 The patient's Zubrod performance status must be 0-3.

3.1.7 Patients must be at least 18 years of age.

3.1.8 Mandatory Imaging Studies: Must be done 45 or fewer days prior to study entry

3.1.8.1 MRI or CT scan of the brain including the entire skull base and all areas of tumor extension

3.2 **Exclusion Criteria**

3.2.1 Patients who are unable to undergo general anesthesia

3.2.2 Patients who are unable to undergo placement of a stereotactic head frame

3.2.3 Patients who are unable to provide informed consent

3.2.4 Patients who are pregnant or nursing

3.2.5 Patients with severe kidney dysfunction

3.2.6 Patients who have contraindications to MRI, such as implanted pacemaker device

3.2.7 Patients with diagnosis of pituitary carcinoma

3.3 **Informed consent**

3.3.1 Patients must provide study-specific informed consent prior to ANY protocol specific procedures

3.3.2 Patients must agree to having the radioactive seeds remain permanently in place after implantation except for rare occasions (i.e. seed migration, as listed below in section 6.8.2), due to the potential morbidity of seed removal otherwise

3.3.3 All patients must be willing and capable to provide informed consent to participate in the protocol

3.3.4 Patient is available for study related assessments and management at the treating institution for the duration of the study

## 4 PRETREATMENT EVALUATIONS/MANAGEMENT (This section lists baseline evaluations needed before the initiation of protocol treatment)

4.1 **Required evaluations**

4.1.1 History and physical examination to include full neurologic assessment (cranial nerve evaluation, confrontational visual field examination, strength assessment, sensory assessment, reflex assessment, gait and balance assessment)

4.1.2 Zubrod performance status (Appendix III)

4.1.3 Baseline visual acuity assessment

4.1.4 Baseline Humphrey visual field assessment

4.1.5 Baseline audiometry exam

4.1.6 Baseline neurocognitive assessment using the mini-mental state examination (MMSE), the Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test: parts A & B, and the Controlled Oral Word Association Test (COWAT)

4.1.7 Assessment of hormone levels (ACTH, AM cortisol, TSH, free T4, testosterone, LH, FSH, IGF-1, GH, prolactin)

4.1.8 Serum creatinine, CBC, platelets, electrolyte panel, PT/INR, PTT

4.1.9 Urine pregnancy test for females (if childbearing age) within one week of study entry

4.1.10 Baseline quality of life evaluation using the European Organization for Research and Treatment of Cancer 30-item core quality of life questionnaire (EORTC QLQ C-30), the brain specific quality of life module (EORTC QLQ BN20)

4.1.11 Baseline assessment for monitoring the cost-utility of treatment will be assessed by using the brief five-item EuroQol (EQ-5D)

## 5 REGISTRATION PROCEDURES

### 5.1 Preregistration

5.1.1 Diagnostic Review

5.1.1.1 There are no requirements for central review of the pathology or radiographic imaging studies used for initial diagnosis

5.1.2 Accreditation

5.1.2.1 Facilities

5.1.2.1.1 Facilities should be in place for performing stereotactic procedures as well as for handling radioactive seeds

5.1.2.2 Equipment

5.1.2.2.1 MRI facilities that are ACR certified

5.1.2.3 Training of Personnel

5.1.2.3.1 Personnel should have performed a certain number of stereotactic procedures as well as transsphenoidal surgeries.

### 5.2 Registration

5.2.1 Contact information

5.2.1.1 Name of Registrar (affiliated with the Clinical Research Office, CRO)

5.2.1.2 Address

5.2.1.3 FAX

5.2.1.4 email

5.2.2 Procedures

5.2.2.1 Enrolling investigator must review eligibility checklist and sign/date at bottom that all criteria have been met.

5.2.2.2 FAX or carry the enrollment form to the Registrar

5.2.2.3 A unique patient participation ID will be assigned

5.2.2.4 Eligibility will be confirmed by CRO Personnel

5.2.2.5 Successful completion of preregistration activities will be confirmed by the CRO Personnel

5.2.2.6 Treatment assignments will be conveyed to the treating investigator

## 6 RADIATION THERAPY

### 6.1 Technical Factors

6.1.1 Physical factors

6.1.1.1 Iodine-125 ($1^{125}$) radioactive seeds (or available isotope with similar energy for gamma decay (i.e. $Cs^{131}$) with prior approval of study PI) will be used for interstitial implantation

6.2 **Simulation**

6.2.1 Patient positioning

6.2.1.1 Patients will be positioned in a stable position supine with a headrest. A knee sponge maybe used for comfort. Use of a facemask for immobilization is not required.

6.2.2 Image acquisition

6.2.2.1 Formal simulation should be carried out with computed tomography (CT) scanning from the vertex to approximately cervical vertebrae #2. CT will be the primary image platform for targeting and treatment planning. The planning CT scans must be done with *IV* contrast unless the patient has allergic problems with contrast or has renal insufficiency. Contrast will allow better distinction between tumor and adjacent vessels, or other non-involved tissues. MRI should also be used for tumor/target localization, as appropriate, when it is likely that they will aid in optimizing simulation (i.e., differentiating target vs uninvolved tissues). MRI imaging will be performed with techniques and frequency consistent with the standard of care for evaluation and follow-up of the disease process. The scans will be ordered as routine pituitary fossa evaluations which include T1 weighted images with and without contrast. Preferred MRI acquisition would also include thin cut contrast enhanced T1 weighted 3-D SPGR images acquired in the coronal plane with fat saturation and subsequently reconstructed in the axial and sagittal planes to better distinguish extent of tumor in the skull base. Various T2 weighted images and/or other sequences will be per the discretion of the supervising neuroradiologist for an optimal, patient appropriate routine study.

6.2.2.2 Axial acquisitions with gantry 0 degrees will be required with spacing ≤ 1.0 mm between scans in the region of the tumor. Images will be transferred to the treatment planning computers via direct lines, disc, or tape.

6.3 **Seed Calibration and Handling**

6.3.1 The seeds will be received and inventoried according to each institution's policy and procedures in a manner consistent with federal or state regulations. A random sampling of at least 10% of the seeds shall be calibrated in such a manner that there is direct traceability to either the NIST or an AAPM ADCL for the I-125 seed, as described by AAPM Report TG 40, paragraph V. A. 2. The measured activity will be compared against the vendor's statement of activity. If the seeds in sterile absorbable material are used, then one seed from every 5 packets will be removed and calibrated.

6.4 **Treatment planning**

6.4.1 Targets (per ICRU 62)

6.4.1.1 Gross tumor volume (GTV) is outlined to correspond to the visible tumor as seen on CT or CT fused with other imaging platforms. The GTV may be disjointed.

6.4.2 Dosimetry

6.4.2.1 Pre-plan

6.4.2.1.1 The determination of the number of seeds, their activity, and location to be implanted will be determined by the volume of the GTV. Implant locations that are achievable via transsphenoidal, transcranial or transfrontal approaches will be used.

6.4.2.1.2 A "point dose" will be defined as a dose to 0.035 cc of tissue rather than the planning system's definition of a point.

6.4.2.2 Prescription Dose and Volume

6.4.2.2.1 The prescribed dose is the dose that the oncologist intends to deliver and is the dose entered into the treatment record. For the purposes of this protocol, the prescribed dose is 50 Gy to the margin of the GTV. The prescription dose must cover at least 90% of the GTV. The volume encompassed with prescription isodose volume should be recorded on the appropriate data form.

6.4.2.3 Minimum Target Dose

6.4.2.3.1 For the purposes of this protocol, the minimum target dose will be defined as the minimum dose to the GTV. This can be determined by an evaluation of the dose distribution in each CT image containing the adenoma. The minimum dose to the GTV should be at least 80% of the prescriptions dose (40 Gy)

6.4.2.4 Hot Spot (High Dose) Volume

6.4.2.4.1 For the purposes of this protocol, the hot spot volume is defined as the volume enclosed by 150% of the prescribed dose (75 Gy) is the hot spot volume. This dose level must occur within the GTV. The high dose volume in all axial planes shall be reported on the appropriate data form.

6.4.2.5 Low Dose Volume

6.4.2.5.1 For the purposes of this protocol, the low dose volume will be defined as the volume encompassed by the 50% of prescription Isodose volume (25 Gy). The low dose volume should be reported on the appropriate form.

6.4.2.6 Dose Volume Histograms

6.4.2.6.1 A DVH for the GTV should be calculated in 5 Gy increments and presented in tabular form

6.4.2.6.2 A DVH for the optic pathway, as defined in the region of the adenoma such that the high dose volume of the implant is included, shall be calculated in 5 Gy increments and presented in tabular form

6.4.2.6.3 A DVH for the brain stem, as defined in the region of the adenoma such that the high dose volume of the implant is included, shall be calculated in 5 Gy increments and presented in tabular form

6.4.2.6.4 A DVH for the hippocampi as defined in the region of the adenoma such that the high dose volume of the implant is included, shall be calculated in 5 Gy increments and presented in tabular form

6.4.3 Organs at Risk (OAR)

6.4.3.1 Optic nerve limit. The dosimetry should be constructed so that the optic nerves, chiasm, and proximal optic radiations receive no more than the prescription dose (50 Gy) to any point along the optic pathway. Exceeding this by more than 5% is a major protocol violation.

6.4.3.2 Hippocampi limit. The dosimetry should be constructed so that the hippocampi receive no more than the prescription dose (50 Gy) to any point. Exceeding this by more than 5% is a major protocol violation.

6.4.3.3 Contouring OARs

The OARs must be appropriately contoured so that dose volume histograms can be generated. Fusion of 3D-SPGR MRI to the treatment planning CT would assist greatly in the delineation of the OARs and is therefore highly recommended. Contouring instructions are described in the table

| Serial Tissue | Contouring Instructions | Endpoint (≥Grade 3) |
|---|---|---|
| Optic Pathway | Contour as one structure including both sides from posterior globe, including chiasm, to proximal optic radiations | neuritis |
| Hippocampi | Contour bilateral hippocampi as one structure as per the RTOG hippocampi sparing proctocol | memory loss |
| Cochlea | Each side separately, include at least 3 CT slices | hearing loss |
| Brainstem (not medulla) | Superiorly from incisura, midbrain and pons only, one structure | cranial neuropathy |
| Cerebellum | Contour entire cerebellum to cerebellar peduncles | Ataxia |

6.5 **Radiation Therapy Treatment**

6.5.1 Radioactive seeds will be implanted via transsphenoidal, transcranial or transfrontal approach with the assistance of a stereotactic head frame (see section 7 for more details).

6.6 **Post-Operative Evaluation**

6.6.1 The post-implant CT shall be taken the same day or following day after the implant. This scan will also be used to assess for any bleed post-operatively. The patient shall be positioned in a similar position as the pre-implant planning scan.

6.6.2 As defined above, the post-implant CT definition of the adenoma is the GTV. As a minimum, dose distributions shall be calculated on each image on which the GTV is defined. The post-implant dosimetry form shall be completed. This form requires the determination of the minimum dose of the GTV for each axial image on which the GTV is defined, the dimensions of the high dose area on each axial image on which the GTV is defined, the dimensions of the low dose area on each axial image on which the GTV is defined, and tabular DVH's for the adenoma and high dose regions of the optic tract, brainstem and hippocampi in 5 Gy increments.

6.6.3 The evaluation criteria are as follows:

- Per Protocol: greater than or equal to 90% of the GTV receives at least the prescription dose (50 Gy) and 99% of the GTV should receive at least 40 Gy. The maximum dose to the dense optic pathways and hippocampi is no more than 50 Gy
- Variation, Acceptable: greater than or equal to 70% of the GTV receives at least 50 Gy and 99% of the GTV receives between 35-40 Gy. The dense optic pathway and hippocampi receives 50-52 Gy.
- Deviation, Unacceptable: The 50 Gy Isodose covers less than 70% of the target or the minimum dose to 99% of the GTV is under 35 Gy. The dense optic pathway and hippocampi maximum dose is more than 52 Gy.

6.7 **(Radiation Therapy Compliance)**

6.7.1 Accreditation Compliance

6.7.1.1 All criteria listed in Section 5 must be completed to the satisfaction of the Principal Investigators in order to be accredited. Upon completion of the criteria, a letter will be sent to institutions informing them of accreditation for the study. No institution will be allowed to enroll patients without accreditation.

6.8 **Radiation Therapy Adverse Events**

6.8.1 General approach

6.8.1.1 Radiation associated adverse events will be categorized and scored according to the Common Toxicity Criteria (version 4.0) available from the United States National Institutes of Health website (http://ctep.info.nih.gov).

6.8.1.2 Relation to therapy (e.g., unrelated, possibly, probably, or definitely related) will be made. In trials with multiple modalities (e.g., surgery and radiation), an attempt will be made to distinguish which therapy was causative. However, in some circumstances this will not be possible.

6.8.2 Seed Migration

6.8.2.1 Follow up imaging on the scheduled intervals listed below (9.1.1) will be used to monitor the position of the implanted radioactive seeds. There is the potential for the seeds to migrate and/or change position in response to shrinkage of the tumor secondary to treatment. This change in location of the seeds could potentially cause an increased dose to OARs. If this occurs, then measures should be attempted to move or remove the seed which has migrated if the treating physician determines appropriate. Seeds that are removed will be handled and disposed of as per institutional policy

6.8.3 Radiation-Induced Necrosis

6.8.3.1 Radiation-induced necrosis (RIN) is part of a series of clinical syndromes related to CNS complications of radiotherapy. These syndromes occur in a distinct chronologic order and have characteristic pathophysiology. While the term radiation necrosis is used to refer to radiation injury, pathology is not limited to necrosis and a spectrum of injury patterns may occur. Clinical symptoms

as well as follow-up imaging studies will be used to assess for the presence of radiation-induced necrosis. If RIN is suspected, observation, steroids or hyperbaric oxygen therapy could be used for treatment as determined appropriate by the treating physician.

## 6.9 Radiation Therapy Adverse Event Reporting

### 6.9.1 Definition of an Adverse Event (AE)

6.9.1.1 Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

### 6.9.2 Definition of a Serious Adverse Event (SAE)

6.9.2.1 Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

6.9.2.2 Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered an SAE experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

### 6.9.3 Electronic Institutional Review Board (eIRB)

6.9.3.1 eIRB constitutes a mechanism for reporting serious adverse events to the UTSW IRB for reporting purposes.

6.9.3.2 Any adverse event equivalent to CTC V.4 grade 3, 4, or 5 or which precipitates hospitalization or prolongs an existing hospitalization must be reported regardless of designation (expected or unexpected) along with the attribution. This includes all deaths that occur within 30 days after the patient was discontinued from the study regardless of attribution AND any events that occur beyond 30 days and are considered probably related to treatment.

6.9.3.3 SAE reports must be completed (the CRF plus information describing the event, the grade, and the attribution) within 48 hours of the investigator's awareness of the occurrence of the event.

6.9.3.4 Attribution of an event can be categorized as:

- Not Related
- Possibly Related
- Probably Related
- Definitely Related

6.9.3.5 Adverse events (below grade 3) do not need to be submitted immediately. Rather, they should be documented in the Adverse Events Clinical Report Form (CRF) along with a brief description of the event, grade, and attribution).

All SAE reports should be made via FAX transmission to:

**Department of Radiation Oncology**
**Clinical Research Office**
**The University of Texas Southwestern Medical Center**
**Attention: Jean Wu, Project Manager**
**FAX #: 214-648-5923**

## 7 OTHER THERAPY (INCLUDING SURGERY)

### 7.1 Surgery

7.1.1 Transsphenoid approach for placement of radioactive seeds

7.1.1.1 The patient will be placed under general anesthesia. The stereotactic head frame will then be placed. A MRI scan of the brain with gadolinium contrast will then be obtained. A Mayfield headholder will be used to retain the stereotactic head frame. As this point, examination of the nose using nasal endoscope to assess for the best route will be performed. Good access into the sphenoid sinus with visualization of the sella should be obtained. Placement of the radioactive seed will be placed using the stereotactic head frame utilizing coordinates obtained from the pre-implant planning scan. Lateral X-rays should be obtained to verify the correct level of the seed and also to make sure the seed stayed in place once the introducer was removed.

7.1.2 Transcranial approach for placement of radioactive seeds

7.1.2.1 Patient preparation and set-up will be similar as that mentioned above for a transsphenoidal approach. After the stereotactic coordinates are confirmed, a skin knife will be used to expose the skull. A hand drill is used to perforate through the bone and dura. The radioactive seed will then be implanted with an introducer and conformation of location as well as seed retention after removal of the introducer should be confirmed by fluoroscopic x-ray. The craniotomy site will then be closed in an appropriate fashion.

7.1.3 Following surgical placement of the seeds, the frame should be removed and the patient monitored for an appropriate amount of time to assess for any potential acute post-operative complications.

### 7.2 Permitted Supportive Therapy

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

- Antiemetics
- Anticoagulants
- Antidiarrheals
- Analgesics
- Hematopoietic Growth Factors
- Herbal products
- Nutritional supplements

## 8 SPECIMEN SUBMISSION

### 8.1 Pathology review

8.1.1 Central pathology review

8.1.1.1 A copy of the initial pathology report (if available) defining the eligible histological diagnosis must appear in the treatment record.

8.1.1.2 No central pathology review is part of this protocol

### 8.2 Tissue submission for translational research

8.2.1 Investigational nature of translational research

8.2.1.1 Initially serum will be collected in order to build proteomic profiles of treatment recurrence, control, and toxicity, however, with time there may be other analytical methodologies that are not yet devised. Blood cells will be processed and RNA and DNA collected. Ultimately, gene expression and genotyping will be performed and correlated with treatment outcome or normal tissue response.

8.2.2 Tissue collection

8.2.2.1 Serum will be collected and frozen for subsequent analysis

8.2.2.2 Whole blood will be drawn [20 ml per collection timepoint: 10 ml from red top and 10 ml from lavender top tubes] using standard procedure in order to collect lymphocytes as well as plasma serum. Blood will be processed using standard procedure immediately after it is collected and then stored at -70 to -80 degrees C. The samples will be kept indefinitely or until exhausted.

8.2.2.3 Collection Timepoints

1. Within 1 week prior to the first treatment (baseline)
5. 6 months after completing the treatment

8.2.2.4 For serum collection, the following materials must be provided: the date of collection of the serum, timepoint of blood collection, type of sample, the protocol number, and the patient's study specific study-ID number.

8.2.2.5 Submit materials for Translational Research to:

**Michael Story, Ph.D.**
**UT Southwestern Medical Center at Dallas**
**5323 Harry Hines Blvd, Dallas, Texas 75390**
**(214) 648-5557**
**Michael.Story@utsouthwestern.edu**

8.2.3 Confidentiality and Storage

8.2.3.1 Upon receipt, the specimen is labeled with the protocol number and the patient's assigned study-identification number only. The database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

8.2.3.2 Specimens for translational research will be stored for an indefinite period of time (or until exhausted) and may be used for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be destroyed.

8.2.3.3 Specimen will be stored at the UT Southwestern Medical Center Division of Molecular Radiation Biology laboratories (NC 7.206) and the UT Southwestern Tissue Repository.

## 9 PATIENT ASSESSMENTS

9.1 Study Parameters per Study Calendar found in Appendix II

9.1.1 Monitor for change in size of adenoma

9.1.1.1 The pre-treatment dimensions of the pituitary adenoma will be determined by using the pre-treatment MR images and measuring the adenoma. The maximum craniocaudal and transverse diameters of the adenoma will be measured on the coronal plane, while the anteroposterior diameter will be measured on the sagittal plane. These measurements will be determined by the radiation oncologist and the neurosurgeon and be reported in millimeters (mm) and overall volume of the adenoma ($mm^3$).

9.1.1.2 The schedule for follow-up MR imaging studies will be every 3 months following seed implantation for the first two years, every six months for the next two years and then yearly afterwards. Measurements as stated above in 9.1.1.1 will be obtained for each imaging study.

9.1.2 Monitor for improvement in Humphrey visual field testing

9.1.2.1 Pre-treatment Humphrey visual field testing will be performed by a neuro-ophthalmologist assessing the visual field status of each eye of the patient

9.1.2.2 Each eye will be counted as data point in which future measurements will be compared

9.1.2.3 The schedule for follow-up Humphrey visual field testing will be every 6 months following seed implantation for the first two years, then yearly afterwards.

9.1.3 Monitor for potential adverse effects

9.1.3.1 Specific toxicities that will be monitored are cerebrospinal fluid rhinorrhea, radiation-induced necrosis, changes in visual field deficits, changes in visual acuity, changes in auditory acuity, worsening headaches, and development of neurocognitive and/or short-term memory deficits

- Cerebrospinal fluid rhinorrhea will be assessed for at every follow up appointment
- Radiation-induced necrosis will be assessed for by utilizing clinical symptoms and radiographic imaging at every follow-up appointment
- Changes in visual field deficits will be assessed by performing confrontational visual field testing at every follow-up appointment (a more detailed assessment of visual fields will be obtained by using Humphrey visual field testing as outlined in 9.1.2)
- Changes in visual acuity will be assessed in conjunction with the Humphrey visual field testing by a neuro-ophthalmologist at the scheduled times as outlined in 9.1.2
- The presence of worsening headaches will be assessed at every follow up appointment. A scale of 1-10 will be used to determine the severity of the headaches.
- Development of neurocognitive and/or short-term memory deficits will be assessed by using the following testing modalities: the mini-mental status exam (MMSE), the Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test: parts A & B, and the Controlled Oral Word Association Test (COWAT). These will be administered every 12 months.

9.1.4 Endocrinological Evaluation

9.1.4.1 Pre-treatment hormone levels will be determined for ACTH, AM cortisol, TSH, free T4, testosterone, FSH, LH, IGF-1, GH, prolactin. Any abnormal values will be corrected for with appropriate supplementation. Follow-up endocrinological evaluations will take place annually.

9.1.5 Quality of Life Assessments

9.1.5.1 Quality of life assessments will take place prior to treatment and then every six months for the first year and then yearly afterwards. The following questionnaires will be utilized for this assessment: the European Organization for Research and Treatment of Cancer 30-item core quality of life questionnaire (EORTC QLQ C-30), the brain specific quality of life module (EORTC QLQ BN20) and

9.1.6 Evaluation of Cost-Utility

9.1.6.1 Evaluation the cost-utility of the treatment arm (in terms of the primary outcome) in comparison with other widely accepted cancer and non-cancer therapies will be assessed by using the brief five-item EuroQol group EQ-5D-3L. Assessments will take place prior to treatment and then every six months for the first year and then yearly afterwards.

9.2 Ongoing Toxicity Assessments

9.2.1 All acute and late adverse events from protocol radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTC) version 4.0. A copy of the CTC v4.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov).

**Please note that this study will not be using separate toxicity scales for acute and late radiation adverse events.**

## 10 DATA COLLECTION

10.1 Submission

10.1.1 Data should be submitted to:

**Department of Radiation Oncology**
**Clinical Research Office**
**The University of Texas Southwestern Medical Center**
**Attention: Jean Wu, Project Manager**
**5801 Forest Park Road**
**Dallas, Texas 75390-9183**
**FAX #: 214-648-5923**

Patients will be identified only by initials (first middle last) and a unique study ID number assigned to each study participant; if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name. Participating sub-sites must remove or black-out identifiers from source documentation that is sent to UTSW.

10.1.2 Summary of Data Submission

| Item | Due |
|---|---|
| Demographics | Within 2 weeks of study entry |
| Eligibility and Entry Characteristics including baseline H&P and labs | Within 2 weeks of study entry |
| Baseline Humphrey Visual field testing | Within 2 weeks of study entry |
| Baseline audiometry | Within 2 weeks of study entry |
| Baseline Neurocognitive Assessments | Within 2 weeks of study entry |
| Baseline QOL Assessments | Within 2 weeks of study entry |
| Dosimetry information | Within 1 week after completion of post-implant CT imaging |
| Follow-up H&P data | follow-up at 1, 3, 6, 9, 12 months, then every 6 months to 4 years; then annually for years 4-10 |
| Adenoma Measurements | follow-up at 3, 6, 9, 12 months, then every 6 months to 4 years; then annually for years 4-10 |
| Follow-up Humphrey Visual field testing | follow-up at every 6 months to 2 years; then annually for years 2-10 |
| Follow-up Endocrine Evaluation | follow-up at every 12 months to 10 years |
| Follow-up Neurocognitive Assessment | follow-up at every 12 months to 10 years |
| QOL Assessment | follow-up at every 6 months to 1 year, then annually for years to 2-10 |
| Adverse Event assessment | follow-up at 1, 3, 6, 9, and 12 months, then every 6 months to 4 years; then annually for years 4-10 |

## 11 STATISTICAL CONSIDERATIONS

11.1 Primary Endpoint

11.1.1 The primary endpoint of this study is to determine the rate of partial (>30% reduction in GTV) or complete responses occurring within one year of therapy. This will be assessed by measuring the adenoma in three dimensions, as well as determining the total volume, on pre-treatment and follow-up imaging studies. The percent change in size and volume of the adenoma will then be calculated by subtracting the post-treatment measurements from the pre-treatment measurements then divided by the pre-treatment measurements and then multiplied by 100. The mean, median and standard deviation of the percent change will be determined.

11.2 Secondary Endpoints

11.2.1 Change in Humphrey Visual Fields

11.2.1.1 Data for each eye will be obtained before and after treatment. Visual fields will be reviewed by a neuro-ophthalmologist for any signs of improvement or deterioration.

11.2.2 Toxicities

11.2.2.1 Specific toxicities that will be monitored are cerebrospinal fluid rhinorrhea, radiation-induced necrosis, changes in visual field deficits, changes in visual acuity, changes in auditory acuity, worsening headaches, and development of neurocognitive and/or short-term memory deficits

11.2.3 Progression Free Survival

11.2.4 Change in QOL Assessments

11.2.4.1 Scoring of each assessment tool will be conducted as per each individual tool's scoring instructions

11.3 Sample Size

11.3.1 *Overview*: The primary goal of this study is to monitor shrinkage in adenoma size and volume following treatment.

11.3.2 ***Sample Size Derivation*:** The predicted partial or complete response rate (PR+CR) of treated subjects at a follow-up interval of 12 months is the determinant of sample size. A PR + CR rate of of 10% or less would be considered insufficiently low for further investigation of this treatment, whereas a PR + CR probability of 50% or higher will be considered worthy of future investigation. If the true PR + CR rate is 50%, a sample size of 10 patients will provide 87% power to detect a significantly higher RTS than 10% with an alpha level of 0.025. To assure an adequate number of evaluable patients, allowing for a small number of patients who would be lost to follow-up or otherwise found non evaluable, a total of up to 12 patients will be enrolled. This analysis applies to both cohorts (those with and without previous radiation therapy)

**The sample size of this study will not exceed 24 patients**.

11.3.3 There will be an early stopping rule for unexpected toxicity. If at any point during the study more than 1/6 of patients treated to date experience study treatment-related grade 4-5 toxicity of any kind, study enrollment will be suspended. Treatment related events include those related or possibly related to therapy.

11.4 Patient Accrual and Study Duration

11.4.1 It is expected that it will take approximately three to five years to complete the study. The analysis for tumor shrinkage will be carried out after each follow-up and collectively after each patient has had 365 days (i.e., 12 months) of follow-up. Study-related data will be stored for 5 years after termination of the study when accrual is no longer taking place and all patients have discontinued follow-up procedures. Blood drawn for translation research will be kept indefinitely or until exhausted.

11.5 Analysis Plan

11.5.1 Interim Reports

11.5.1.1 Interim reports will be updated at least every six months until the results of the study are published. In general, the interim reports will contain information about patient accrual rate with projected completion dates of the trial, status of QA review and compliance rate of treatment per protocol, and the frequencies and severity of toxicity.

11.5.1.2 *The Analysis of Tumor Shrinkage*: This analysis will be carried out when each patient has had at least 730 days (i.e., 24 months) of follow-up. The percent change in size and volume of the adenoma will then be calculated by subtracting the post-treatment measurements from the pre-treatment measurements then divided by the pre-treatment measurements and then multiplied by 100. The mean, median and standard deviation of the percent change will be determined.

11.5.1.3 *Estimation of Secondary Endpoints Related to the Efficacy*: Cumulative incidence approach will be used to estimate the progression free survival. For any individual patient, progressive disease (PD) within the treated lesion will be scored as PD for that patient

11.6 Gender and Minorities

11.6.1 In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have also considered the possible interaction between race and treatments. The projected gender and minority accruals are:

**Projected Distribution of Gender & Minorities**

| Ethnic Category | Sex/Gender | | |
|---|---|---|---|
| | Females | Males | Total |
| Hispanic or Latino | 4 | 4 | 8 |
| Not Hispanic or Latino | 4 | 12 | 16 |
| Ethnic Category: Total of all subjects | 8 | 16 | **24** |
| **Racial Category** | | | |
| American Indian or Alaskan Native | 0 | 0 | 0 |
| Asian | 0 | 2 | 2 |
| Black or African American | 4 | 6 | 10 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| White | 4 | 8 | 12 |
| More than one race | 0 | 0 | 0 |
| Racial Category: Total of all subjects | 8 | 16 | **24** |

## 12 DATA SAFETY MONITORING PLAN

12.1 Purpose and Scope

12.1.1 The purpose of the Radiation Oncology Data and Safety Monitoring Plan is to ensure that clinical trial data is accurate and valid and to ensure the safety of trial participants.

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

12.2 Procedures

12.2.1 Clinical trials are assessed for safety on a continual basis throughout the life of the trial. All SAE's and any AEs that are unexpected and possibly/likely related to study participation are reported to UTSW IRB through an electronic research system per UTSW IRB guidelines.

12.2.2 All clinical trials are reviewed on monthly basis for enrollment. All local SAEs are reviewed by Radiation Oncology DSMC monthly for severity and attribution. For investigator-initiated trials, all SAEs at affiliated institutions are monitored as local SAEs. The principle investigator and study coordinator will present a study treatment summary and SAEs for review. Source documents will be available for the DSMC members during the review. NCI Common Toxicity Criteria Version 4 will be used for grading and attributing adverse events.

12.2.3 If the SAE occurs on a multi-institutional clinical trial coordinated by the Radiation Oncology Clinical Research Office, the Clinical Research Manager or primary coordinator ensures that all participating sites are notified of the event and resulting action, within one (1) working day of the determination.

12.2.4 Interim Stopping Rules - Stopping for toxicity or efficacy will be related to dose limiting toxicity as described in the statistical section.

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**APPENDIX I**
**STUDY PARAMETER TABLE**

| | Pre-Entry | Months Following Treatment | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 30 | 36 | 42 | 48 | Every 12 months for years 4-10 |
| **History and Physical Exam** | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **MRI Brain** | X | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Weight** | X | | | X | | | | | X | X | X | X | X | X | X |
| **Humphrey Visual Field Test** | X | | | X | | X | | X | | X | | X | | X | X |
| **Visual Acuity** | X | | | X | | X | | X | | X | | X | | X | X |
| **Audiometry** | X | | | | | | | | | | | | | | |
| **Pregnancy test (if applicable)** | X | | | | | | | | | | | | | | |
| **Endocrinological Evaluation** | X | | | | | X | | | | X | | X | | X | X |
| **Creatinine, CBC, platelets, PT/INR, PTT, Serum Chemistry** | X | | | | | | | | | | | | | | |
| **Neurocognitive Assessment** | X | | | | | X | | | | X | | X | | X | X |
| **Blood Draw for Translational Research** | X[a] | | | | | | | | | | | | | | |
| **Informed consent** | X | | | | | | | | | | | | | | |
| **QOL Assessment** | X | | | X | | X | | | | X | | X | | X | X |
| **Adverse event evaluation** | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

[a] week prior to implant

## APPENDIX II

### ZUBROD PERFORMANCE SCALE

| | |
|---|---|
| **0** | **Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).** |
| **1** | **Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).** |
| **2** | **Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).** |
| **3** | **Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).** |
| **4** | **Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).** |
| **5** | **Death (Karnofsky 0).** |

### KARNOFSKY PERFORMANCE SCALE

| | |
|---|---|
| **100** | **Normal; no complaints; no evidence of disease** |
| **90** | **Able to carry on normal activity; minor signs or symptoms of disease** |
| **80** | **Normal activity with effort; some sign or symptoms of disease** |
| **70** | **Cares for self; unable to carry on normal activity or do active work** |
| **60** | **Requires occasional assistance, but is able to care for most personal needs** |
| **50** | **Requires considerable assistance and frequent medical care** |
| **40** | **Disabled; requires special care and assistance** |
| **30** | **Severely disabled; hospitalization is indicated, although death not imminent** |
| **20** | **Very sick; hospitalization necessary; active support treatment is necessary** |
| **10** | **Moribund; fatal processes progressing rapidly** |
| **0** | **Dead** |

## APPENDIX III

**Post-Implant Dosimetry Data Form**

Patient:

Physician:

Source: I-125, model XXXX
Doses are based upon TG 43 Dosimetry

Date of Pre-Implant CT study:

Date of Implant:

Date of Post-Implant CT study:

Basic Dosimetry Information

1. average activity per seed as measured by institution:
   - Activity: mCi Date:

2. midpoint apparent activity stated by the vendor:
   - Activity: mCi Date:

3. number of seeds used:

4. number of needles used:

5. Prescribed dose: 50Gy TG 43 dosimetry

6. Peripheral dose: Gy TG 43 dosimetry

**Post Implant CT Analysis**

Date of Implant:
Date of Post Implant CT Study:

1. Adenoma is defined on ____ slices.
2. Seeds are defined on ____ slices.

**Analysis of each CT image**

| Slice | Min Dose to Adenoma (GTV) in Gy | Dimensions of: High Dose Area (cm x cm) | Low Dose Area (cm x cm) |
|---|---|---|---|
| 1 | | | |
| 2 | | | |
| 3 | | | |
| 4 | | | |
| 5 | | | |
| 6 | | | |
| 7 | | | |
| 8 | | | |

| | | | |
|---|---|---|---|
| 9 | | | |
| 10 | | | |
| 11 | | | |
| 12 | | | |

**Dose Volume Histogram Analysis**
Doses are based on TG 43 dosimetry

| Dose/Gy | Volume/%Adenoma | Volume/%Optic pathway | Volume/%brain stem | Volume/%memory pathway |
|---|---|---|---|---|
| 10 | | | | |
| 20 | | | | |
| 30 | | | | |
| 40 | | | | |
| 50 | | | | |
| 60 | | | | |
| 70 | | | | |
| 80 | | | | |
| 90 | | | | |
| 100 | | | | |
| 110 | | | | |
| 120 | | | | |
| 130 | | | | |
| 140 | | | | |
| 150 | | | | |
| 160 | | | | |
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| 280 | | | | |
| 290 | | | | |
| 300 | | | | |
| 310 | | | | |
| 320 | | | | |
| 330 | | | | |
| 340 | | | | |
| 350 | | | | |
| 360 | | | | |
| 370 | | | | |
| 380 | | | | |
| 390 | | | | |
| 400 | | | | |

# Appendix IV

## Neurocognitive Battery: Background Information and Test Instructions

There are three immediate recall responses, one delayed recall response, and one delayed recognition response in the HVLT-R. The response is the number of words the patient can recall out of 12 words for recall responses and the difference of the listed words correctly and incorrectly recalled for recognition response. The response from Trail Making Test, parts A & B is the time takes to finish each test less than 3 and 5 minutes, respectively. There are three responses for the COWAT, and each response is the number of words starting with a provided letter of the alphabet that the patient can produce in one minute.

**Testing: General Information**

1. Testing should be completed in one session. Test instructions must be followed verbatim with every patient at every assessment visit.
2. Tests should be administered in the following order to every patient and at each assessment visit: HVLTR Part A (Learning Trials); Trail Making Test Part A; Trail Making Test Part B; COWAT; HVLT-R Part B (Delayed Recall); and the HVLT-R Part C (Delayed Recognition).
3. Follow the instructions on the Forms Packet Index before submitting the forms.
4. All test results are recorded on the Neurocognitive Evaluation Summary Form , which is found in the Forms Packet. Study/case-specific labels must be applied to all forms.
5. **Note**: Sites should keep all original test records, and test results must remain on file at the institution as source documentation pending request for submission..
6. Patients should not be given copies of their tests to avoid learning the material between test administrations.
7. The HVLT-R and the COWAT have alternate forms or versions in order to reduce the effects of practice. See the test instructions below for the versions to be administered at pre-treatment and subsequent sessions. The forms should continue to be alternated in this order for the duration of the study. The forms packet will contain alternate versions of these neuropsychological tests.

Before dismissing the patient, thank him/her for their cooperation. Remind the patient of their next appointment and that these tests will be repeated.

In the event that a patient cannot complete a given test, please write the reason(s) on the test form AND the data summary form.

**Testing: Specific Instructions**
**Note:** Administer the tests in the following order to every patient at each assessment visit.

**1. HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)**

This test has three parts and six alternate forms (only the first 4 forms will be used in this study):
**Part A - Free Recall:** Complete the three learning trials first
**Part B - Delayed Recall:** Complete after Trail Making Tests and COWAT
**Part C - Delayed Recognition:** Complete after Delayed Recall

**Part A – Free Recall: Trial 1**
**Examiner*: "I am going to read a list of words to you. Listen carefully, because when I am through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?"***
• Read the words at the rate of one word every 2 seconds.

***Examiner: "OK. Now tell me as many of those words as you can remember*."**
• Check off the words the patient recalls on the form.

• If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
• If the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
• If not, move on to trial 2. Later, you can record the number of words that were correctly repeated on the summary form.

**Part A – Free Recall: Trial 2**
**Examiner*: "Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including the words you told me the first time."***
• Read the words at the rate of one word every 2 seconds.
• Check off the words the patient recalls on the form.
If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
• If the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
• If not, move on to trial 3. Later, you can record the number of words that were correctly repeated on the summary form.

**Part A – Free Recall: Trial 3**
**Examiner*: "I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me."***
• Read the words at the rate of one word every 2 seconds.
• Check off the words the patient recalls on the form.
• If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
• If the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
• **Do not tell the respondent that recall of the words will be tested later.**
• Record the time on the clock that you *complete* 'Part A – Free Recall' (for example, 1:00 p.m.) on the designated space on the HVLT-R form.

**2. TRAIL MAKING TEST [Timed Test]**

**Part A – Sample*:*** Place the Sample A worksheet flat on the table, directly in front of the patient *(the bottom of the worksheet should be approximately six inches from the edge of the table).* Give the patient a black pen and say:
**Examiner*: "On this page* (point) *are some numbers. Begin at number 1* (point to 1) *and draw a line from 1 to 2* (point to 2), *2 to 3* (point to 3), *3 to 4* (point to 4), *and so on, in order, until you reach the end* (point to the circle marked END). *Draw the lines as fast as you can. Ready, begin."***

If the patient completes Sample A correctly, and in a manner demonstrating that s/he understands what to do, proceed immediately to Test A. If the patient makes a mistake on Sample A, point out the error and explain it.
The following explanations of mistakes serve as illustrations:
• ***This is where you start (point to number 1).***
• ***You skipped this circle (point to the circle omitted).***
• ***You should go from number 1 to 2, 2 to 3, and so on, until you reach the circle marked END.***

If it is clear that the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample A, take his/her hand and guide him/her through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on he copy. Then say:

**Examiner*: "Remember, begin at number 1 (*point to 1*) and draw a line from 1 to 2 (*point to 2*), 2 to 3 (*point to 3*), 3 to 4 (*point to 4*) and so on, in order, until you reach the circle marked END (*point*). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."***

If the patient does not succeed, or it becomes evident that s/he cannot do the task, DISCONTINUE testing **and** indicate the corresponding reason on the Trail Making Data Sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

**Part A – Test:** After the patient has completed Sample A, place the Part A test worksheet directly in front of the patient and say:
**Examiner*: "Good! Let's try the next one. On this page are numbers from 1 to 25. Do this the same way. Begin at number 1 (*point*) and draw a line from 1 to 2 (*point to 2*), 2 to 3 (*point to 3*), 3 to 4 (*point to 4*) and so on, in order, until you reach the circle marked END (*point*). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."***
• Start timing as soon as the instruction is given to "begin"
• Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred
• The patient must complete the test in **3 minutes** or less.
• **DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END".**
• Collect the worksheet and record the time to completion on the Trail Making Data Sheet in minutes and seconds
• If the patient does not complete the test within **3 minutes** terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Data Sheet indicating the reason the test was terminated and the last correct number reached on the test.

**Part B – Sample:** Place the Sample B worksheet flat on the table, directly in front of the patient (the bottom of the worksheet should be approximately six inches from the edge of the table) and say:
**Examiner*: "On this page (*point*) are some numbers and letters. Begin at number 1 (*point to 1*) and draw a line from 1 to A (*point*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*), 3 to C (*point to C*) and so on, in order, until you reach the end (*point to the circle marked END*). Remember, first you have a number (*point to 1*), then a letter (*point to A*), then a number (*point to 2*), then a letter (point to B), and so on. Draw the lines as fast as you can. Ready, begin."***

If the patient completes Sample B correctly, and in a manner demonstrating that s/he understands what to do, proceed immediately to Part B. If the patient makes a mistake on Sample B, point out the error and explain it.
The following explanations of mistakes serve as illustrations:
• ***You started with the wrong circle. This is where you start (point to number 1)***
• ***You skipped this circle (point to the circle omitted)***
• ***You should go from number 1 (*point*) to A (*point*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*) and so on, until you reach the circle marked END (*point*).***

If it is clear the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample B, take their hand and guide them through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:
**Examiner*: "Now you try it. Remember, begin at number 1 (*point to 1*) and draw a line from 1 to A (*point to A*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*) and so on, in order, until you reach the circle marked END (*point*). Ready, begin."***

If the patient does not succeed or it becomes evident that s/he cannot do the task, DISCONTINUE testing **and** indicate the corresponding reason on the Trail Making Data Sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

**Part B – Test:**
After the patient has completed Sample B, place the Part B Worksheet directly in front of the patient and say:
**Examiner*: "Good! Let's try the next one. On this page are both numbers and letters. Do this the same way. Begin at number 1 (*point*) and draw a line from 1 to A (*point to A*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*), 3 to C (*point to C*) and so on, in order, until you reach the circle marked END (*point*). Remember, first you have a number (*point to 1*), then a letter (*point to A*), then a number (*point to 2*), then a letter (*point to B*), and so on. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can. Ready, begin."***
• Start timing as soon as the instruction is given to "begin".
• Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred
• The patient must complete the test in **5 minutes** or less.
• **DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END".**
• Collect the worksheet and record the time to completion on the Trail Making Data Sheet in minutes and seconds.
• If the patient does not complete the test within 5 minutes terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Data Sheet indicating the reason the test was terminated and the last correct number or letter reached on the test.

**3. CONTROLLED ORAL WORD ASSOCIATION TEST (COWAT) [Timed Test]**

This test has three parts (letters) and two alternate forms.

**Examiner*: "I am going to say a letter of the alphabet, and I want you to say as quickly as you can all of the words that you can think of that begin with that letter. You may say any words at all, except proper names such as the names of people or places. So you would not say 'Rochester' or 'Robert'. Also, do not use the same word again with a different ending, such as 'Eat,' 'Eats,' and 'Eating.'***

***"For example, if I say 's,' you could say 'sit,' 'shoe,' or 'show.' Can you think of other words beginning with the letter 's'?"***

Wait for the patient to give a word. If it is a correct response, say ***"good"***, and ask for another word beginning with the letter "s". If a second appropriate word is given, proceed to the test itself.

If the patient gives an inappropriate word on either occasion, correct the patient, and repeat the instructions. If the patient then succeeds, proceed to the test.

If the patient fails to respond, repeat the instructions. If it becomes clear that the patient does not understand the instructions or cannot associate, stop the procedure, and indicate the reason(s) on the scoring sheet.

If the patient has succeeded in giving two appropriate words beginning with the demonstration letter, say:

**Examiner*: "That is fine. Now I am going to give you another letter. Again, say all of the words beginning with that letter that you can think of. Remember, no names of people or places, just ordinary words. Also, if you should draw a blank, I want you to keep on trying until the time limit is up and I say STOP."***

***"You will have a minute for each letter. The first letter is '___'"*** (see scoring sheet).

****Allow exactly one minute for each letter.****
• If the patient discontinues before the end of the time period, encourage him/her to try to think of more words.

• If he/she is silent for 15 seconds, repeat the basic instruction and the letter (e.g., **"Tell me all the words you can think of that begin with a "c"**).
• No extension on the time limit is made in the event that instructions are repeated.
• Continue the evaluation with the remaining two letters, allowing one minute for each.

Recording and Scoring:
• The record sheet provides lines on which the patient's responses can be entered *(e.g., write in the word that is said by the patient)*. If his/her speed of word production is too fast to permit verbatim recording, a "+" should be entered to indicate a correct response.
• Incorrect responses either should not be recorded or, if recorded, should be struck through with a line.
• If the patient provides more responses than there are lines on the record sheet, keep writing the responses *(or a "+")* elsewhere on the record sheet.
• Count all the correct responses. The number of correct words should be indicated below each column on the recording sheet and on the summary data form.

Comments on scoring:
• Note: It can be helpful for the first several patients and for patients known to be fast with their word production to tape record the session for transcription at a later time.
• The instructions include a specific prohibition against giving proper names or different forms of the same word. Therefore, inflections of the same word *(e.g., eat-eating; mouse-mice; loose-loosely; ran-run-runs)* are not considered correct responses.
• Patients often give both a verb and a word derived from the verb or adjective *(e.g., fun-funny; sadsadness)*. These are not considered correct responses. On the other hand, if the word refers to a specific object *(e.g., foot-footstool; hang-hanger),* it would be counted as a correct answer.
• Many words have two or more meanings *(e.g., foot; can; catch; hand)*. A repetition of the word is acceptable IF the patient definitely indicates the alternative meaning to you.
• Slang terms are OK if they are in general use.
• Foreign words *(for example, pasta; passé; lasagna)* can be counted as correct if they can be considered part of English vocabulary *(for example, in general use or found in the dictionary).*
• If the test is discontinued or omitted, please mark this on the bottom of the test form and indicate the reason on the Tests Discontinued/Not Done CRF

## 4. HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)

### Part B – Delayed Recall
• **DO NOT READ THE WORD LIST AGAIN.**
• Record the time on the clock that you *start* 'Part B – Delayed Recall' (for example, 1:20 p.m.) on the designated space on the HVLT-R form.
• Administer 'Part B – Delayed Recall' **after** completing **all** Trail Making Tests and the COWAT. There should be at least **15 minutes** between 'Part A' and 'Part B'. If the time is too short, allow the patients to complete a questionnaire.

**Examiner: "*Do you remember that list of words you tried to learn before? Tell me as many of those words as you can remember."***
• Check the box on the corresponding line of the HVLT-R worksheet for each word the patient accurately recalls.
• If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
• If the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
• If not, record the number of words that were correctly recalled on the summary form.

### Part C – Delayed Recognition

**Examiner*: "Now I'm going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list or "No" if it was not. Was [word] on the list?"***

• Check either the "**Y"** (Yes) or "**N"** (No) box next to each word to indicate the patient's response.
• Guessing is allowed.
• If the test is discontinued or omitted, please mark this on the bottom of the test form and indicate the reason on the Tests Discontinued/Not Done CRF.

The score for this portion of the HVLT-R is the number of list words (i.e., words that in CAPS) correctly identified ("yes" response) minus the number of non-list words (i.e., words in lower case) incorrectly identified ("yes" response). Therefore, the actual score can range from –12 *(no list words identified and all non-list words identified)* to +12 *(all list words identified and no non-list words identified)*.

## Appendix V

## Quality of Life Assessments

The EORTC quality of life questionnaire (QLQ) is an integrated system for assessing the health related quality of life (QoL) of cancer patients participating in international clinical trials. The core questionnaire, the QLQ-C30, is the product of more than a decade of collaborative research. Following its general release in 1993, the QLQ-C30 has been used in a wide range of cancer clinical trials, by a large number of research groups.

General principles of scoring

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items.
Each of the multi-item scales includes a different set of items - no item occurs in more than one scale.
All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.
Thus a **high score for a functional scale** represents a *high / healthy level of functioning*, a **high score for the global health status / QoL** represents a *high QoL*, but a **high score for a symptom scale / item** represents a *high level of symptomatology / problems*.
The principle for scoring these scales is the same in all cases:
1. Estimate the average of the items that contribute to the scale; this is the *raw score*.
2. Use a linear transformation to standardise the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

For more details and statistical evaluation, please see: http://www.eortc.be/home/qol/files/SCManualQLQ-C30.pdf

## Appendix VI

## Cost Effectiveness

Almost every incremental improvement in survival or progression-free survival comes at a cost. The cost is both financial and experienced in terms of quality of life. Measurement of primary outcomes such as freedom from progression and the most important aspects of human functioning and quality of life will permit a summary equation allowing for differences in quality of life, clinical outcomes, and cost to be incorporated into one equation. This equation is the Quality Adjusted Life Year (QALY) and a study-specific modification, the Quality Adjusted Freedom From Progression Year (QAFFPY). The QALY has been modified in a similar manner for different treatments where survival is not the primary outcome. Much of the work in modifying the QALY began in ophthalmology, where sight-years, not life-years, are the outcome of interest. Examples of modifications to the QALY have included incremental cost per vision-year gained to assess the cost effectiveness of photodynamic therapy with verteporfin for age-related macular degeneration, costs per sight-year saved with screening for diabetic retinopathy, cost-utility analysis for treatments of retinal detachment associated with severe proliferative vitreoretinopathy, and the cost-utility of cataract surgery. However, the QALY has been used in other studies where survival is not the primary outcome of interest, such as the costeffectiveness of memantine in the treatment of patients with moderately severe to severe cognitive impairment from Alzheimer's and cochlear implantation for patients unable to gain effective speech recognition with hearing aids. We will model costs using Medicare reimbursement and measure utilities with the brief five-item EuroQol (EQ-5D).

The EQ-5D is a method for obtaining valuations (utilities) of health-related quality of life (HRQOL) to be used as an adjustment to survival and in the cost-utility analysis. Developed in 1987, the EQ-5D is used by investigators and the pharmaceutical industry throughout the United States, Europe, and Asia. It is one of only several measures recommended for use in cost-effectiveness analyses by the Washington Panel on Cost Effectiveness in Health and Medicine. The EQ-5D instrument is intended to complement other forms of QOL measures, and it has been purposefully developed to generate a generic cardinal index of health, thus giving it considerable potential for use in economic evaluation. The argument by some that a generic measure does not capture some of the disease- or treatment-specific concerns of a given study misses the point. This cost-effectiveness analysis is being done for purposes of exploring the means to inform macro (health policy, payer) decision making, not micro (individual) decision making. The findings from the disease-specific QOL instruments and treatment-related side effect QOL instruments described above will help inform individual decision making. The role of the EQ-5D is to measure HRQOL at a macro level, in the same metric as it has been measured across numerous diseases, including cancer.

This instrument gives us the ability to compare across and within diseases the “big picture” of what the experts who developed the EQ-5D considered the primary health states of interest to humans: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Further, there is no standardized measure to assess and compare disease-specific utilities across or within diseases. Unlike the EQ-5D, the actual content of standard gamble (SG) and time tradeoff (TTO) methods vary widely among studies and are subject to wide variations in amount and type of information presented, message framing, and visual aids, making replication of utilities with the SG or TTO extremely difficult. Therefore, using the EQ-5D, an exploratory aim is to evaluate the cost-utility of the treatment arm demonstrating the most significant benefit (in terms of the primary outcome), in comparison to other widely accepted cancer and non-cancer therapies. We will also assess cost-utility among the arms to assess which therapy dominates. We will assess the value added of the summary score known as a Quality Adjusted Life Year (QALY), and for this study the Quality Adjusted FFP Year, that combines benefits of duration of freedom from progression (FFP) and decrements of quality of life with financial cost of increasingly aggressive and costly therapy.

The EQ-5D has been used across numerous disease sites, including cancer. For example, the EQ-5D mean score for 95 patients with NSCLC (93% male, mean age 62 years) was 0.58 (SD 0.32) as measured by the questionnaire and 0.58 (SD 0.20) as measured by the visual analogue scale (VAS) version. The EQ-5D has been used to assess QALYs and the economic value of prostate cancer screening, and treatment of pain related to prostate cancer metastasis. Further, the EQ-5D was used in a recent study to estimate the

economic value of the welfare loss due to prostate cancer pain by estimating the extent to which pain affects health-related quality of life among patients with prostate cancer. Health status and economic outcomes were modeled among a well-defined population of 200,000 Swedish prostate cancer patients. Health utility ratings (using the EQ-5D) were obtained from a subset of 1,156 of the prostate cancer patients. A descriptive model showed that optimal treatment that would reduce pain to zero during the whole episode of disease would add on average 0.85 quality-adjusted life years (QALY) to every man with prostate cancer; the economic value of this welfare loss due to prostate cancer pain was approximately $121,240,000 per year.

Quality-Adjusted Survival and Freedom from Progression

Quality-adjusted survival and freedom from progression can be defined in the same manner, by the weighted sum of different time episodes added up to a total quality-adjusted life-year or freedom from progression–year [**U**= sum of quality (**qi**) of health states **K** times the duration (**si**) spent in each health state].

Cost-Effectiveness and Cost-Utility

Cost-utility will be analyzed for planned publication at two time points: 1) at 1 year post-therapy, looking at initial treatment costs and quality of life and 2) at five years post-therapy. The cost-utility analysis will be done after the primary endpoint results are published.

Measurement of Costs

Direct medical costs fall into three categories: 1) initial therapy costs; 2) costs of managing the most common side effects as determined by this study; and 3) costs of managing recurrence. Costs for interstitial radiotherapy will be determined using CPT coding and Medicare reimbursement rates. Costs of common management strategies of the most common side effects documented in this study (e.g., Imodium® for diarrhea) will be estimated from regional costs per unit. Costs for managing recurrence will assume the following salvage therapies: hormone therapy and chemotherapy. Costs will include professional fees, cost/inpatient day, drugs, and supplies. Direct non-medical costs such as the cost of work lost or of transportation will not be measured. Incremental differences in costs and outcomes will be compared for the different alternatives and for the dominant alternative to other established therapies documented in the literature.

The EQ-5D is a two-part self-assessment questionnaire. The first part consists of 5 items covering 5 dimensions (mobility, self care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a three point Likert scale (1-no problems, 2-moderate problems, and 3-extreme problems). There are 243 (=35) health states. The second part is a visual analog scale (VAS) valuing the current health state measured by 100 point scale with 10 point interval (0-worst imaginable health state, 100-best imaginable health state).

## Appendix VII

## Risks to Subjects

| Procedure | Risks | Measures to Minimize Risks |
|---|---|---|
| History and physical exam (H&P) | Discovery of previously unknown condition | Will be performed by MD and/or nurse practitioner with oncology experience. |
| MR imaging / CT imaging of the brain | Discovery of previously unknown condition/recurrence or progression of pituitary adenoma; discomfort | Will be performed by nurse/technician with radiology experience |
| Blood draws (at all study timepoints) | Discomfort, bleeding, bruising, dizziness, fainting, infection | Blood will be drawn by an experienced phlebotomist. |
| Zubrod Performance status evaluation | Discomfort, psychological stress of answering personal questions | Subjects informed that they may refuse to answer, take a break, or discontinue participation at any time |
| Neurocognitive evaluation | Discomfort, psychological stress of answering personal questions | Subjects informed that they may refuse to answer, take a break, or discontinue participation at any time |
| QOL assessment | Discomfort, psychological stress of answering personal questions | Subjects informed that they may refuse to answer, take a break, or discontinue participation at any time |
| Interstitial seed placement | Hemorrhage, cerebral spinal fluid leak, neurological deficits<br><br><u>Constitutional</u>:<br>likely: fatigue | Participants will be educated and asked to inform study personnel if encounter symptoms. |
| FAX transmittal of case report forms (CRFs) to primary site | Loss of privacy | Sensitive patient information will be blacked-out. CRFs will only be identified by subject initials and unique, study identification number before fax transmittal. |
| Unforeseen risks | E.g., unpredictable interaction between radiotherapy and concomitant medications | Strong encouragement to report any difficulties and keep researchers aware of any change in medications |