PHASE IV TRIAL TO USE STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR HEAD AND NECK TUMORS

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PHASE IV TRIAL TO USE STEREOTACTIC BODY RADIOSURGERY (SBRT) FOR BENIGN AND MALIGNANT HEAD AND NECK TUMORS

SCHEMA

R Stereotactic Body Radiotherapy (SBRT)

E Benign Head and Neck Tumors: Paraganglioma
Chordoma
G Chondrosarcoma

I Suggested Dose-Fractionation: 14-16 Gy / 1 fraction
18-21 Gy / 3 fractions (6-7 Gy per fraction)
S 25-45 Gy / 5 fractions (5-9 Gy per fraction)

T Malignant Head and Neck Tumors: Nasopharynx Cancer
Unresectable Cancers
E
Suggested Dose-Fractionation: 8-12 Gy / 1 fraction
R 12-18 Gy / 3 fractions (4-6 Gy per fraction)
35-45 Gy / 5 fractions (7-9 Gy per fraction)

Chemotherapy

Chemotherapy may be given at the discretion of the patient's medical oncologist. However, ideally chemotherapy, including immune-modifying drugs, should not have been given within 2 weeks of starting radiation and should not resume until at least 2 weeks after completing radiation.

Eligibility

- Patient age $\geq$ 18 years
- Zubrod performance status of 0-3
- Benign head and neck tumors such as paragangioma (ex. Glomus jugulare, glomus tympanicum, carotid body tumors),chordoma, chondrosarcoma, angiofibroma
- Malignant head and neck cancers such as invasive squamous cell carcinoma, adenocarcinoma, nasopharyngeal carcinoma, salivary gland cancers, and sarcomas
- No pregnant or lactating women (negative pregnancy test for women of child-bearing age)
- Signed study-specific consent form

1.0 Introduction

Stereotactic Body Radiotherapy (SBRT) is a novel technique in the radiation oncology community. SBRT has evolved as a treatment option for malignant skull base lesions, and can be used to treat recurrent head and neck cancers (1-6).

Nasopharynx cancer has been treated effectively with radiation therapy. Due to recent advances in radiation oncology and the combined use of chemotherapy, improvements in local control and overall survival have been obtained over the last decade. Local recurrence still occurs and generally the outcome for salvage treatment has been poor. Due to the anatomical location of the nasopharynx, recurrent nasopharynx cancer is difficult to treat. SBRT has been use successfully to treat recurrent disease (3-6). In addition to recurrent disease, SBRT has been used successfully as a boost after external beam radiation to safely increase the radiation dose to tumors (7,8).

For patients with locally recurrent head and neck cancer arising form the oral cavity, oropharyx, larynx, or hypopharynx treatment options may be limited. For patients who have received prior radiation therapy, additional standard external beam radiation therapy may not be an option. For patients who develop recurrence at the skull base, complete surgical resection usually can not be achieved. Patients may experience symptoms which can diminish their quality of life. Pain is a common symptom of recurrent head and neck cancer. Stereotactic body radiotherapy may provide excellent palliation for patients with recurrent head and neck cancers. Most patients who receive SBRT have excellent palliation of pain. In addition, some patients may achieve long term local control (9-11).

Chordomas are locally aggressive and destructive tumors with high recurrence rates. Chondrosarcomas arise from the skull base and tend to affect lower cranial nerves. Complete surgical resection is rarely feasible for these lesions. Various modalities of fractionated radiation therapy have been used to increase local control. Stereotactic body radiotherapy delivers more conformal radiation with greater radiobiological effect than conventional radiation therapy. Compared to conventional radiation therapy, SBRT may reduce toxicity to normal surrounding structures and potentially cause fewer complications. Martin et al. from the University of Pittsburg reported on 28 patients treated with SBRT as a boost after external beam radiation or as the sole treatment. The median follow up was 7 years. The five year local control rate for chondrosarcomas was 80%. The five year local control rate for chordomas was 62%. One patient developed mild dizziness and nausea which was controlled with a two week course of corticosteroids. No long term side effects were reported. The authors concluded that SBRT is an important treatment option for chordomas and chondrosarcomas(12-15).

2.0 Objectives

This study will evaluate the local control rates as well as acute and late toxicity rates of stereotactic body radiotherapy (SBRT) for the treatment of benign and malignant head and neck tumors.

2.1 Hypothesis

2.1.1 For selected patients with primary or recurrent head and neck tumors, stereotactic body radiotherapy (SBRT) is technically feasible with acceptable complication rates.

2.2 Study Design

2.2.1 Single site, non-randomized, prospective, phase IV sudy

2.2.2 Composed of 3 patient groups:

- Benign tumors, such as paraganglioma (ex. Glomus jugulare, glomus tympanicum, carotid body tumor) chordoma, chondrosarcoma, as the sole treatment or to gross residual disease after maximal safe resection
- Malignant tumors, such as nasopharynx cancer and squamous cell carcinoma, after initial external beam radiation (Residual Disease Group)
- Unresectable malignant tumors, such as nasopharynx cancer and squamous cell carcinoma, adenocarcinoms, and sarcomas which are recurrent after prior radiation (Primary RT Group)

2.2.3 Data collected will include baseline patient demographics, pathology data, radiation therapy procedure, tumor recurrence data, and toxicities.

2.2.4 Follow up data will be collected during the patient's standard office visits. The anticipated duration of this study is 5 years.

2.3 End Points

2.3.1 Primary endpoints will be local control rate and complication rate

- Local recurrence is defined as cancer recurrence within the target volume.
- Local control rate will be evaluated by imaging techniques, physical exam and biopsy, if applicable.
- Evaluation of complication rates (see Section 9.3 for definitions)

2.3.2 Secondary endpoint will be overall survival

3.0 Patient Selection

3.1 Eligibility Criteria

3.1.1 Patient age $\geq$ 18 years

3.1.2 Zubrod performance status of 0-3

3.1.3 Benign head and neck tumors such as paragangliomas (ex. Glomus jugulare, glomus tympanicum carotid body tumor), chordoma, chondrosarcoma

3.1.4 Malignant head and neck cancers such as invasive squamous cell carcinoma, adenocarcinoma, nasopharyngeal carcinoma, salivary gland cancers, and sarcoma

3.1.5 No pregnant or lactating women (negative pregnancy test for women of child-bearing age)

3.1.6 Signed study-specific consent form

3.2 Exclusion Criteria

3.2.2 Pregnant or lactating women, due to potential exposure of the fetus to RT and unknown effects of RT on lactating females

3.2.3 Patients with psychiatric or addictive disorder that would preclude obtaining informed consent

4.0 Pretreatment Evaluation

4.1 Patient history, including prior radiation and chemotherapy treatments
4.2 Physical examination with the location and palpable size of the lesion in cm
4.3 CT scan of involved head and neck region
4.4 Other imaging studies are optional, including PET

5.0 Simulation

5.1 Fabrication of a custom mask and bite block immobilization device or placement of a stereotactic head frame
5.2 Treatment planning CT scan acquired in treatment position with patient's head immobilized

6.0 Radiation Therapy

6.1 Target Definition

6.1.1 Gross tumor volume (GTV) is contoured on the planning CT scan. If available, Diagnostic CT scan, MRI and/or PET images may be utilized to construct the GTV by registering them to the planning CT dataset.

6.1.2 At the discretion of the treating radiation oncologist, the GTV margins may be expanded to form the planning target volume (PTV).

6.2 Dose-Specification

6.2.1 Radiation beams will conform to the PTV outline without additional margin and the dose will be prescribed to the isodose line (IDL) that covers at least 95% of the PTV, which is typically around 80%.

6.2.2 SBRT dose-fractionation scheme will be chosen at the discretion of the treating radiation oncologist, but the normal tissue dose constraints should be maintained. Suggested dose-fractionation schemes, derived from the available literature, are listed below. Also included are the corresponding biologic equivalent dose (BED) for each based on the linear-quadratic model:

	SBRT scheme	*BED[1] (α/β=10)*	*BED[2] (α/β=3)*	*Equivalent 2 Gy/Fx Dose[1] (α/β=10)*	*Equivalent 2 Gy/Fx Dose[2] (α/β=3)*
Paraganglioma	14 Gy x 1	33.6 Gy	79.3	28	47.6
	15 Gy x 1	37.5 Gy	90	31.3	53.9
	16 Gy x 1	41.6 Gy	101	34.7	60.5
	6 Gy x 3	28.8 Gy	54	24	32.4
	7 Gy x 3	35.7 Gy	70	29.9	41.9
	5 Gy x 5	37.5	66.7	31.3	40.0

Chordoma Chondrosarcoma	6 Gy x 5 7 Gy x 5 8 Gy x 5 9 Gy x 5	48 59.5 72 85.5	90 117 147 180	40 49.6 60 71.3	53.9 70 88 108
Malignant Cancer (Residual Disease)	8 Gy x 1 9 Gy x 1 10 Gy x 1 11 Gy x 1 12 Gy x 1 4 Gy x 3 5 Gy x 3	14.4 17.1 20 23.1 26.4 16.8 22.5	29.3 36 43 51.3 60 28 40	12 14.3 16.7 19.3 22 14 18.8	17.6 21.6 25.8 30.1 35.9 16.8 23.9
Malignant Cancers (Recurrent)	8 Gy x 1 9 Gy x 1 10 Gy x 1 11 Gy x 1 12 Gy x 1 13 Gy x 1 14 Gy x 1 4 Gy x 3 5 Gy x 3 6 Gy x 3 7 Gy x 5 8 Gy x 5 9 Gy x 5	14.4 17.1 20 23.1 26.4 29.9 33.6 16.8 22.5 28.8 59.5 72 85.5	29.3 36 43 51.3 60 69.3 79.3 28 40 54 117 147 180	12 14.3 16.7 19.3 22 24.9 28 14 18.8 24 49.6 60 71.3	17.6 21.6 25.8 30.1 35.9 41.6 47.6 16.8 23.9 32.4 70 88 108

[1]Cancers are assumed to have an α/β ratio of approximately 10

[2]Normal tissues are assumed to have an α/β ratio of approximately 3

6.3 Normal Tissue Dose Constraints

6.3.1 Normal tissue dose constraints will depend on whether nearby critical normal tissues have received prior external beam radiation, what dose they received, and the time between prior radiation and the current SBRT treatment course. These dose limits will ultimately be determined by the treatment radiation oncologist. For patients who have received prior radiation therapy, every effort should be taken to limit the cumulative doses to adjacent critical normal tissues as follows based on standard fractionation schemes (1.8-2 Gy per day):
Spinal cord – D_{max} = 50 Gy
Brainstem – D_{max} = 60 Gy
Optic Nerves – D_{max} = 50 Gy
Optic Chiasm - D_{max} = 54 Gy

6.3.2 For patients in whom SBRT is planned following initial standard-fractionation wide-field external beam radiation (Residual Disease Group), the initial radiation course should be designed to limit exposure to adjacent critical normal tissues as follows:
Spinal cord – D_{max} = 40 Gy

Optic Apparatus – D_{max} = 50 Gy
Brainstem – D_{max} = 50 Gy

6.3.3 For patients who have not received prior radiation therapy, the following dose limits should be maintained:

Structure	1 Fraction	3 Fractions	5 Fractions
Optic Chiasm	8 Gy D_{max}	12 Gy D_{max}	14 Gy D_{max}
Optic Nerve	8 Gy D_{max}	12 Gy D_{max}	14 Gy D_{max}
Brainstem	14 Gy D_{max}	22 Gy D_{max}	27 Gy D_{max}
Spinal Cord	8 Gy to < 0.5 cc 10 Gy to < 0.3 cc 12 Gy to < 0.15 cc	18 Gy D_{max}	22 Gy D_{max}
Brachial Plexus	14 Gy D_{max}	24 Gy D_{max}	25 Gy D_{max}
Internal Carotid Artery in Cavernous Sinus	25 Gy D_{max}	32 Gy D_{max}	35 Gy D_{max}
Oculomotor Nerves in Cavernous Sinus	30 Gy D_{max}	32 Gy D_{max}	35 Gy D_{max}
Esophagus	15 Gy D_{max}	24 Gy D_{max}	30 Gy D_{max}
Skin	15 Gy D_{max}	24 Gy D_{max}	30 Gy D_{max}

7.0 Stereotactic Body Radiotherapy Treatment Delivery

7.1 Premedication

The decision to premedicate a patient prior to head and neck SBRT is at the discretion of the treating radiation oncologist. Most patients typically do not need premedication. The following are a list of agents that have been used by some investigators to potentially reduce patient discomfort and possibly prevent acute and/or late toxicity if used as premedication prior to SBRT.

7.1.1 Corticosteroids (Decadron 4 mg PO or equivalent) 15-60 minutes prior to each fraction for the intended purpose of modulating immediate inflammatory effects.

7.1.2 Analgesic premedication to avoid general discomfort during long treatment durations.

7.1.3 Anti-anxity medication for patient comfort during long treatment duration

7.2 Treatment

7.2.1 The medical physics staff will perform routine quality assurance checks on the treatment machine to ensure that the mechanical isocenter stability is within specification (ie. diameter $\leq$ 1.5 mm).

7.2.2 The medical physics staff will perform patient-specific quality assurance measurements to ensure that the treatment plan is deliverable and that the dose distribution is accurate.

7.2.3 The patient will be positioned in the custom immobilization device on the Hexapod® treatment couch and aligned with the in-room lasers.

7.2.4 Daily CT localization of the GTV isocenter is required prior to each fraction. Once the patient is properly positioned, a cone-beam CT of the treatment area is acquired, fused, and aligned to the treatment planning CT. Translational and rotational adjustments of patient positioning are performed as indicated. If adjustment are required, an orthogonal (ex. AP and LATERAL) set of electronic portal images is then obtained prior to treatment to confirm proper alignment of the isocenter.

7.2.5 Either multiple coplanar or noncoplanar static gantry angle intensity-modulated fields or rotational arcs will be utilized.

7.2.6 Only photon (x-ray) beams will be used, preferably in energies of 6 MV.

8.0 Drug Therapy

8.1 The use of chemotherapy is left to the discretion of the medical oncologist.

8.2 Chemotherapy agents during radiation is not allowed. If chemotherapy is planned, it should ideally not have been given within 2 weeks of starting radiation and should not resume until at least 2 weeks after completing radiation.

9.0 Patient Assessment

9.1 Study Parameters

The following are suggested patient follow-up intervals and evaluations that may be performed to either assess for treatment toxicity or tumor response to SBRT:

Assessment	Pre-Rx	Post-Rx 6 wk	Post-Rx 3 mo	Post-Rx 6 mo	Post-Rx 9 mo	Post-Rx 1 yr
History & Physical	X	X	X	X	X	X[b]
Weight	X	X	X	X	X	X[b]
Disease status	X	X	X	X	X	X[b]
Toxicity Assessment		X	X	X	X	X[b]
Pregnancy test	X[a]					
CT and/or MRI (head and neck)	X	X	-	X	-	X[b]

a if clinically appropriate

b clinical examination, late toxicity, and disease status assessment at 3 month intervals for first year, then at the discretion of the treating radiation oncologist

9.2 Response Criteria

9.2.1 CT scan of the soft tissues of the neck with IV contrast (MRI may be used)
- Local recurrence is defined as tumor recurrence within the planning target volume. If necessary, a PET/CT scan may be used to aid in diagnoses local tumor recurrence.

9.2.2 PET/CT scan
- May be obtained at the discretion of the treating radiation oncologist if there is uncertainty on the diagnostic CT scan as to the disease status in the head and neck.

9.2.3 A local recurrence is defined as cancer recurrence within the planning target volume.

9.2.4 Distant metastases will not be considered a treatment failure unless accompanied by local recurrence.

9.3 Toxicity

9.3.1 The investigator will report and record all serious adverse events that occur. Adverse events should be reported using the CTC grading system (Appendix III).

9.3.2 Examples of anticipated acute adverse events include:
- General malaise
- Radiation dermatitis – dryness, tanning, redness, itching
- Localized hair loss
- Mucositis
- External otitis
- Otitis Media
- Xerostomia
- Mastoiditis

- Weight loss
- Pharyngitis
- Vertigo

9.3.3 Examples of anticipated late adverse events include:
- Radionecrosis of the temporal bone, skull base, mandible
- Radionecrosis of brain tissue
- Soft tissue necrosis
- CVA
- Cranial nerve neuropathy
- Ipsilateral hearing loss
- Vocal cord paralysis
- Nasal hemorrhage
- Localized skin fibrosis, edema, and/or ulceration
- Radiation-induced malignancy (ex. Fibrosarcoma)

9.3.4 Reporting of unanticipated or serious adverse events will be reported according to the institutions IRB policy. An unanticipated adverse effect is defined as follows:

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, stereotactic body radiotherapy, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a treatment that relates to the rights, safety, or welfare of subjects.

9.4 Patient Withdrawal from Study

During the course of the study, it is possible that patients may withdraw or be withdrawn from the study. Factors that may lead to a withdrawal from the study may include, but are not limited to the following:

Patient Withdrawal……At any time a patient may voluntarily withdraw from the study. This withdrawal will not affect their future medical treatment or benefits.

Patient Lost to Follow-Up…….Should a patient be classified as lost to follow-up, efforts to contact the patient should be made.

Physician Decision……Should a physician decide that continuing in the study is detrimental to the health and welfare of the patient, the patient may be withdrawn from the study.

Medical Reason……..Should the patient condition deteriorate the patient may be withdrawn from the study to allow for proper medical care.

10.0 Risk/Benefit Analysis

10.1 Risk associated with Stereotactic Body Radiotherapy for head and neck tumors

10.1.1 Acute toxicities reported to occur as a result of SBRT for head and neck tumors include, but are not limited to:
- General malaise
- Radiation dermatitis – dryness, tanning, redness, itching
- Localized hair loss
- Mucositis
- External otitis
- Otitis Media
- Xerostomia

- Mastoiditis
- Weight loss
- Pharyngitis
- Vertigo

10.1.3 Late toxicities reported to occur as a result of SBRT for head and neck tumors include, but are not limited to:

- Radionecrosis of the temporal bone, skull base, mandible
- Radionecrosis of brain tissue
- Soft tissue necrosis
- CVA
- Cranial nerve neuropathy
- Ipsilateral hearing loss
- Vocal cord paralysis
- Nasal hemorrhage
- Localized skin fibrosis, edema, and/or ulceration
- Radiation-induced malignancy (ex. Fibrosarcoma)

10.2 Minimization of Risks

Although the risks outlined in Section 9.3 may occur, the likelihood of serious events occurring is considered uncommon as long as certain precautions are taken. The potential risks have been minimized by strict compliance with normal tissue dose constraints as described in Sections 6.3.

10.3 Potential Patient Benefits

10.3.1 Ability to offer effective aggressive local therapy to patients with recurrent unresectable head and neck cancers who have received prior wide-field radiation

10.3.2 Reduction in amount of radiation delivered to adjacent normal structures

10.3.3 Reduced treatment duration compared to standard-fractionation radiation therapy

10.4 Justification of the Study

Patients who have locally recurrent or persistent malignant head and neck cancer after definitive conventionally fractionated radiation therapy pose a therapeutic challenge since complete surgical resection is often not feasible and surrounding critical normal tissues have typically received close to maximum tolerable radiation doses. High dose, precisely targeted radiation with stereotactic body radiotherapy, which delivers minimal additional radiation dose to nearby normal tissues can produce durable local control and palliation of local symptoms such as pain. In addition, some benign head and neck tumors which are located near the skull base and/or involve critical vasculature also pose a surgical challenge. These tumors appear to have a reasonably high local control probability with radiation therapy. SBRT is advantageous in this setting by limiting the dose to adjacent normal tissues in patients who otherwise have a long life expectancy.

10.5 Statistical Analysis

10.5.1 The overall survival and local control rates will be analyzed.

10.5.2 The incidence rate for any serious adverse events will be calculated.

11.0 References

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12.0 Appendices

12.1 Appendix I

St. John's Mercy Medical Center
Informed Consent for a Clinical Research Study

STUDY TITLE: PHASE IV TRIAL TO USE STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR HEAD AND NECK TUMORS

This is a clinical trial (type of research study). Clinical trials include only patients who choose to take part. This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family and friends before making your decision.

WHAT SHOULD YOU KNOW ABOUT THE RESEARCH DOCTOR?

You should know that your relationship with a research doctor is different from your relationship with your personal doctor. Your personal doctor is treating your specific problem with the hope of a benefit for you. When a doctor is your research doctor, he/she is treating all subjects under a specific protocol to learn about the results of a treatment, and with the understanding that you may or may not benefit from your participation in the study. Be sure to ask questions of the study doctor if you want more information about this relationship.

WHY IS THIS STUDY BEING PERFORMED?

Some head and neck cancers recur locally even after aggressive surgery and/or several weeks of daily radiation therapy, with or without chemotherapy. They often cause significant pain or other troublesome local symptoms such as difficulty eating. These are very often not resectable due to nearby critical normal tissues such as major blood vessels and nerves. The ability to give additional radiation using standard methods is also very limited since there is a maximum dose that normal tissues can tolerate before sustaining permanent injury. Similarly, some benign head and neck tumors which are located near the skull base and/or involve major blood vessels or nerves may also not be easily removed without a high risk for permanent tissue injury.

Recent technological advancements now make it possible to deliver high doses of precisely targeted radiation directly to tumors, while giving very low doses of radiation to nearby normal tissues. This technology is called stereotactic body radiotherapy. A similar technology, termed stereotactic radiosurgery, has been used for many years to successfully treat malignant and benign tumors in the brain. More recently, several institutions have reported successful treatment of both malignant and benign tumors that begin in the upper aerodigestive tract and neck. The purpose of this study is to collect additional data on the effectiveness of stereotactic body radiotherapy for unresectable skull base tumors and locally recurrent head and neck cancer.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Approximately 50 people are expected to participate in this clinical study.

WHAT IS INVOLVED IN THE STUDY?

If you wish to take part in this study, a series of tests will be performed to determine if you qualify for participation in the clinical study. Your physician will ask you a series of questions regarding your medical history and a standard physical exam will be performed. If you are a woman of childbearing age, you may be asked to give a urine or blood specimen so that a pregnancy test can be performed.

If you qualify for the study, you will undergo a radiation treatment planning session called a simulation. At this visit, a custom mask and bite block device will be fabricated or a stereotactic frame will be placed to immobilize your head in the correct position for treatment. Permanent small tattoos may be applied to your skin to aid in positioning your body on the treatment table.

There may be several days between the simulation and the day you begin radiation. During this time, complex radiation treatment planning will be performed by your radiation oncologist and their medical physics staff. You will receive between 1-5 radiation treatments. Your physician will explain your treatment in more detail. Each radiation session may take an hour or longer to complete. After the entire radiation course is complete, you will be given follow-up instructions.

HOW LONG WILL I BE IN THE STUDY?

We anticipate that you will remain in the study for approximately 5 years. After treatment is completed routine follow-up visits will be conducted, typically at 3 month intervals for the first year, then less frequently.

Your physician may decide stop your treatment if: 1) your disease becomes worse, or 2) side effects become very severe, or 3) new scientific developments occur that indicate the treatment is not in your best interest, or 4) your physician believes that this treatment is no longer in your best interest. If your treatment is stopped, your doctor will discuss further treatment options with you.

WHAT ARE THE RISKS OF THE STUDY?

By participating in this study, you are at risk for several possible expected and unexpected side effects associated with stereotactic radiotherapy to the Head and Neck. Some of these are described below; however, there also may be other side effects that we cannot predict. Most side effects go away shortly after the radiation therapy is stopped, but in some cases side effects can be serious, long-lasting, or permanent.

Risks arising from the delivery of stereotactic radiotherapy to the head and neck which may occur shortly after completing treatment may include, but are not limited to:

- Generalized fatigue
- Nausea and/or vomiting
- Loss of appetite
- Hair loss over the treatment area
- Skin redness and/or tanning over the treatment area
- Dry and/or moist skin peeling of skin over the treatment area
- Dry itchy skin
- Thickened saliva and/or dry mouth
- burning sensation with swallowing
- Change in taste
- Inflammation of the outer ear canal and/or inner ear
- Inflammation of the mastoid bone behind the ear
- Pain and ulcers in the mouth and/or throat
- Sore throat which could lead to weight loss

- Dizziness

Risks arising from the delivery of stereotactic radiotherapy to the head and neck which may develop several months to years after completing treatment may include, but are not limited to:

- Radionecrosis/Injury of the temporal bone, skull base, mandible
- Radionecrosis/Injury of brain tissue
- Soft tissue necrosis/damage
- Stroke
- Cranial nerve neuropathy/damage
- Hearing loss
- Vocal cord paralysis
- Nasal hemorrhage/bleeding
- Localized skin hardening, thickening, swelling, and/or ulceration
- Radiation-induced cancer (ex. Fibrosarcoma)
- Low thyroid gland function

I understand that all these side effects are possible. I may experience no side effects, some of them, or most of them. Although I will be closely monitored, not all side effects can be predicated and unforeseen problems can arise. I understand that there may be some unknown or unanticipated risks or discomforts in addition to those specified here.

Reproductive risks: Because even very small doses of radiation can affect an unborn baby, you should not become pregnant while receiving radiation treatment. You should also not nurse a baby while receiving radiation treatment.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be a direct medical benefit to you. However, there have been several trials completed at other institutions that have shown high local control rates after stereotactic body radiotherapy for haed and neck cancer. It is also convenient, requiring only 1-5 radiation sessions and no anesthesia or hospitalization. Toxicity risk has been reported to be fairly low.

WHAT OTHER OPTIONS ARE THERE?

Other treatment options may include chemotherapy, standard-fractionation radiation therapy, or other investigational procedures or medications. Another option is no further therapy. Your doctor can provide information about your disease and the benefits of the different treatments for you. You should feel free to talk with your doctor about your disease and expected outcomes. The doctor involved in your care will be available to answer any questions you have about this program. You are free to ask your doctor any questions concerning this program now or in the future.

You are free to seek care from a doctor of your choice at any time. If you do not take part in, or withdraw from, the study you will continue to receive alternate care.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. This Informed Consent and another document called an "Authorization to Use and Disclose Health Information" control how your health information may be used and disclosed during and after this study. The results of this study may be published or presented at meetings but will not include your name or reveal your identity. To participate in this study, you must sign both the Informed Consent

and the Authorization to Use and Disclose Health Information. Your personal information may be disclosed if required by law.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance carrier. Specifically, you or your insurance carrier will be responsible for the costs of the baseline blood tests, diagnostic imaging studies, stereotactic radiotherapy planning and delivery, and follow-up visits which would otherwise be a standard part of your care. Please ask about any expected added costs or insurance problems. St. John's Mercy Medical Center has personnel that can assist you with this.

Every precaution will be taken to prevent any injury to you during the study. In the event that injury occurs as a result of this study, treatment will be available. You or your insurance carrier will be responsible for the costs of the treatment. No funds have been set aside for compensation in the event of a research related injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will not receive payment for participating in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Your participation is voluntary. You may choose not to take part or may leave the study at any time. Your choice will not affect your doctors from providing care to you. Choosing not to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled.

You will be told of any important new findings developed during the course of your participation in this study that may affect your willingness to continue in the study. The investigator may withdraw you from this study if issues occur that show that you should not continue to participate.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have any questions or concerns regarding this study, or a research-related injury, you may contact one of the Principal Investigators, Dr. Robert Frazier at 314-251-6844 or Dr. Bethany Sleckman at 314-251-7057

For questions about your rights as a research participant, contact Dr. Donald York, Chairman of the St. John's Mercy Medical Center Institutional Review Board (which is a group of people who review the research to protect your rights), at 314-251-6453.

Your doctor understands the importance of your contribution to clinical studies that attempt to improve medical care. Your doctor will make every effort to minimize, control, and treat any problems that may happen as a result of your participation in this study. If you believe that you are injured solely as a result of the study, or if you have questions regarding the study, please contact the Principal Investigator.

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at 1-800-422-6237 or TTY:1-800-322-8615

Visit the NCI's Web Sites:
- Cancer Trials: comprehensive clinical trials information

http://cancertrials.nci.nih.gov

- CancerNet: accurate cancer information including PDQ
  http://cancernet.nci.nih.gov

SIGNATURES

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion. I willingly give my consent to participate in this study. Upon signing this form I will receive a copy. I may also request a copy of the protocol (full study plan).

Participant (sign) _____

Participant (written) _____

Date _____

Principal Investigator _____

Staff Member Performing Consent Process _____

Witness _____

IRB Stamp (This form is INVALID if the stamp is not present.)

12.2 Appendix II

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 signs 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

ZUBROD PERFORMANCE SCALE

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

12.3 Appendix III

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

	GRADE				
Toxicity	**1**	**2**	**3**	**4**	**5**
CONSTITUTIONAL					
Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	-
Fever	100.4-102.2°F	102.3-104.0°F	> 104.0°F for ≤ 24 hr	> 104.0°F for > 24 hr	Death
Weight loss	5 - < 10% of baseline	10 - < 20% of baseline	≥ 20% of baseline; tube feeding or TPN indicated	-	-
PAIN					
Pain due to radiation	Mild pain not interfering with function	Moderate pain: pain or analgesics interfering with function, but not interfering with ADL	Severe pain: pain or analgesics severely interfering with ADL	Disabling	-
Myositis (inflammation or damage of muscle)	Mild pain not interfering with function	Pain interfering with function, but not interfering with ADL	Pain interfering with ADL	Disabling	Death
SKIN					
Radiation dermatitis	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other that skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	
Telangiectasia	Few	Moderate number	Many and confluent	-	-
Ulceration	-	Superficial ulceration < 2 cm size; local wound care; medical intervention indicated	Ulceration ≥ 2 m size; operative debridement, primary closure or other invasive intervention indicated (ex. Hyperbaric oxygen)	Life-threatening consequences; major invasive intervention (ex. Complete resection, tissue reconstruction, flap, grafting)	Death
Induration	Increased density on palpation	Moderate impairment of function not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; ery marked density, retraction or fixation	-	-
SOFT TISSUE					
Fibrosis	Increased density, " spongy" feel	Increased density with firmness or tethering	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL	Life-threatening; disability; loss of limb; interfering with vital organ function	Death
Soft Tissue Necrosis	-	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (ex. Hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (ex. Tissue reconstruction, flap, or grafting)	Death

Osteonecrosis	Asymptomatic, radiographic findings only	Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (minor sequestrectomy)	Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indictaed	Disabling	Death
AUDITORY/EAR					
Hearing	_	Hearing loss not requiring hearing aid or intervention (i.e., not interfereing with ADL)	Hearing loss requiring hearing aid or intervention (i.e., interfereing with ADL)	Profound bilateral hearing loss (>90 dB)	-
Otitis, external ear (non-infectious)	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen, or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis	Necrosis of soft tissue or bone	Death
Otitis, middle ear (non-infectious)	Serous otitis	Serous otitis, medical intervention indicated	Otitis with discharge; mastoiditis	Necrosis of canal soft tissue or bone	Death
GI TRACT					
Dental, periodontal disease	Gingival recession or gingivitis; limited to bleeding on probing; mild local bone loss	Moderate ginival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	-	-
Dental, teeth	Surface stains, dental caries; restorable, without extractions	Less than full mouth extractions; tooth fracture or crown amputation or repair indicated	Full mouth extractions indicated	-	-
Xerostomia	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow > 0.2 ml/min	Symptomatic and significant oral intake alteration (e.g.; copious water, other lubricants, diet limited to purees and /or soft, moist foods) unstimulated saliva flow 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	-	-
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration, or malnutrition; IV fluids indicated < 24 hr	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥ 24 hr	Life-threatening consequences	Death
Vomiting	1 episode in 24 hr	2-5 episodes in 24 hr; IV fluids indicated < 24 hr	≥ 6 episodes in 24 hr; IV fluids or TPN indicated ≥ 24 hr	Life-threatening consequences	Death
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic, and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated < 24 hours	Symptomatic, and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedins, or TPN indicated ≥ 24 hours	Life-threatening consequences (e.g./ obstruction, perforartion)	Death
Mucositis (clinical exam)	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life threatening consequences	Death
Esophagitis	Asymptomatic, pathologic,radiographic or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g. altered dietary habits, oral supplements) IV fluids indicated < 24 hours	Symptomatic and severly altered eating/swallowing (e.g. inadequate oral caloric or fluid intake) IV fluids, tube feedings, or TPN indicated ≥ 24 hours	Life-threatening consequences	Death
Ulceration	Asymptomatic,	Symptomatic; altered GI	Symptomatic and	Life-threatening	Death

	radiographic or endoscopic findings only	function (altered dietary habits, oral supplements); IV fluids indicated < 24 hr	severely altered GI function (inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥ 24 hr	consequences	
Bleeding	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
Perforation	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated < 24 hr	IV fluids, tube feedings, or TPN indicated ≥ 24 hr; operative intervention indicated	Life-threatening consequences	Death
Stricture	Asymptomatic radiographic findings only	Symptomatic; altered GI function (altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated < 24 hr	Symptomatic and severely altered GI function (altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥ 24 hr; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection	Death
Fistula	Asymptomatic; radiographic findings only	Symptomatic; altered GI function (ex. Altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated < 24 hr	Symptomatic and severely altered GI function (ex. Altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥ 24 hr	Life-threatening consequences	Death
Taste Alterations	Altered taste but no change in diet	Altered taste with chage in diet (e.g.; oral supplements); noxious or unpleasant taste; loss of taste	-	-	-
LYMPHATICS					
Lymphatics (head and neck)	Localized to dependant areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g.; difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube	Death
NEUROLOGY					
Brachial plexopathy	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Disabling	Death
CNS Necrosis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL; medical intervention indicated	Symptomatic and interfering with ADL; hyperbaric oxygen indicated	Life-threatening; disabling; operative intervention indicated to prevent or treat CNS necrosis/cystic progression	Death
Myelitis	Asymptomatic, mild signs (e.g.; Babinski's or Lhermitte's sign)	Weakness or sensory loss not interfering with ADL	Weakness or sensory loss interfering with ADL	Disabling	Death
OCULAR/VISUAL					
Cataract	Asymptomatic, detected only on exam	Symptomatic, with moderate decrease in visual acuity (20/40 or better); decreased visual function correctable with glasses	Symptomatic with marked decrease in visual acuity (worse than 20/40); operative intervention indicated (e.g.; cataract surgery)	-	-
Dry eye syndrome	Mild, intervention not	Symptomatic, interfering	Symptomatic or decrease	-	-

	indicated	with function but not interfering with ADL; medical intervention indicated	in visual acuity interfering with ADL; operative intervention indicated		
Rentinopathy	Asymptomatic	Symptomatic, with moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse	-
SECONDARY MALIGNANCY	-	-	Non-life-threatening basal or squamous cell carcinoma of the skin	Solid tumor, leukemia, or lymphoma	Death

12.4 Appendix IV

DEMOGRAPHIC FORM – Page 1 of 1

1. Name _____(last) _____(first)

2. Date of Birth ____/___/_____

3. RT Number _____

4. Race: ☐ Asian ☐ Caucasian ☐ Black ☐ Other, specify _____

5. Zubrod PS: ☐ 0 ☐ 1 ☐ 2 ☐ 3

6. Radiation oncologist: _____

7. Medical oncologist: _____

8. Surgeon: _____

9. Tumor category: ☐ Benign Head and Neck tumor, specify type _____

☐ Malignant Head and Neck Tumor, specify type _____

10. Maximum tumor diameter: _____cm

11. AJCC Staging Classification: ☐ I ☐ II ☐ III ☐ IV ☐ N/A (recurrence)

12. Status of distant metastatic disease:
☐ No distant metastatic disease
☐ Stable distant metastatic disease
☐ Progressive metastatic disease

13. Pretreatment CT scan: Date of CT scan _____

14. Prior Head and Neck radiation: ☐ No ☐ Yes, explain _____

15. Pre-SBRT chemotherapy: ☐ No
☐ Yes, regimen & last cycle date _____

Person completing form: Signature _____ Print Name _____

12.5 Appendix V

TREATMENT FORM – Page 1 of 1

1. Name _____(last) _____(first)

2. RT Number _____

3. Tumor Details:
   Tumor category: ☐ Benign Head and Neck tumor, specify type _____
   ☐ Malignant Head and Neck Tumor, specify type _____

Lesion #	Location	Maximum Diameter (cm)	GTV Volume (cc)	CTV Margin (cm)	PTV Margin (cm)			PTV Volume (cc)
					AP	RL	CC	
1								
2								
3								
4								
5								

4. Treatment Portal Design:
   ☐ Static gantry angle (coplanar), specify number of fields _____
   ☐ Static gantry angle (non-coplanar), specify number of fields _____
   ☐ Dynamic arc (coplanar), specify number of arcs _____
   ☐ Dynamic arc (non-coplanar), specify number of arcs _____

5. Dose-Fractionation Scheme:

Lesion #	Total Dose (Gy)	Dose per Fx (Gy)	# Fx	Prescription IDL (%)	D_{max} (Gy)	$BED_{\alpha/\beta=10}$ (Gy)	$BED_{\alpha/\beta=3}$ (Gy)	CI
1								
2								
3								
4								
5								

6. Dose to Normal Tissues:

   Prior Head and Neck radiation: ☐ No (Table 1) ☐ Yes (Table 2)

   Table 1 (No prior Head and Neck radiation)

Normal Tissue	D_{max} (Gy)
Optic Chiasm	
Optic Nerve	
Brainstem	
Spinal Cord	
Brachial Plexus	

Internal Carotid Artery in Cavernous Sinus	
Oculomotor Nerves in Cavernous Sinus	
Esophagus	
Skin	

Table 2 (Prior Head and Neck radiation)

Normal Tissue	D_{max} (Gy)	Prior RT D_{max} (Gy)*	Total D_{max} (Gy) (D_{max} + Prior RT D_{max})
Optic Chiasm			
Optic Nerve			
Brainstem			
Spinal Cord			
Brachial Plexus			
Internal Carotid Artery in Cavernous Sinus			
Oculomotor Nerves in Cavernous Sinus			
Esophagus			
Skin			

*Estimation of the dose (Gy) may be required

7. Premedication:
   - ☐ None
   - ☐ Anti-nausea, specify drug _____, dose _____ mg,
   - ☐ Decadron, specify dose _____ mg
   - ☐ Analgesics, specify drug _____, dose _____ mg
   - ☐ Acetaminophen, specify dose _____ mg

Person completing form: Signature _____ Print Name _____

12.6 Appendix VI

FOLLOW-UP VISIT FORM – Page 1 of 2

1. Name _____(last) _____(first)

2. RT Number_____

3. Date of Visit: ____/____/_____

4. CT scan date: ____/____/_____

5. Radiation Therapy related adverse events

Adverse Event	CTC V3.0 Grade	Timing	Treatment	Comments
ACUTE				
☐ Fatigue				
☐ Fever				
☐ Nausea				
☐ Vomiting				
☐ Loss of appetite				
☐ Weight loss				
☐ Esophagitis				
☐ Alopecia				
☐ Radiation dermatitis				
☐ Musculoskeletal pain				
☐ Mucositis				
☐ Hoarseness				
☐ Pneumonitis				
☐ Xerostomia				
☐ External otitis				
☐ Otitis Media				
☐ Mastoiditis				
☐ Dizzyness				
LATE				
☐ Radionecrosis of temporal bone, skull base, mandible				
☐ Radionecrosis of brain tissue				
☐ CVA				
☐ Cranial nerve neuropathy				
☐ Hearing loss				
☐ Vocal cord paralysis				
☐ Nasal hemorrhage				
☐ Hypothyroidism				
☐ Esophageal stricture/perforation				
☐ Brachial plexopathy				
☐ Telangiectasia				
☐ Skin Ulceration				
☐ Skin/SubQ Tissue Fibrosis				
☐ Soft Tissue Necrosis				
☐ Radiation-induced Malignancy				

5. Serious adverse event? ☐ No ☐ Yes, submit report to HIC

6. Has systemic therapy been given? ☐ No ☐ Yes

If yes, list therapy

Agent(s)	Start Date	Stop Date
_____	____/____/_____	____/____/_____
_____	____/____/_____	____/____/_____
_____	____/____/_____	____/____/_____

7. CT scan since last follow-up visit? ☐ No ☐ Yes, date ____ / ____ / _____

Tumor Response: ☐ Complete response
☐ Partial response
☐ Stable disease
☐ Progressive disease

8. PET/CT scan since last follow-up visit? ☐ No ☐ Yes, date ____ / ____ / _____

Tumor Response: ☐ Complete response
☐ Partial response
☐ Stable disease
☐ Progressive disease

8. Disease Status

	Date of Diagnosis
☐ No evidence of tumor	
☐ Local recurrence within the treatment volume	____/____/_____
☐ Progressive liver disease outside the treatment volume	____/____/_____
☐ Distant recurrence, specify site _____	____/____/_____

9. Additional treatment for recurrent disease

Surgical excision	☐ Yes ☐ No	Date of surgery ____/____/_____
Chemotherapy, agents _____	☐ Yes ☐ No	Start date ____/____/_____
Other, specify _____	☐ Yes ☐ No	Start date ____/____/_____

10. Death? ☐ No ☐ Yes, date ____/____/_____ Cause? _____

Person completing form: Signature _____ Print Name _____