Stereotactic Radiosurgery for Patients with Recurrent Primary Central Nervous System Lymphoma

Protocol Number:

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1. PROTOCOL SUMMARY

**Title:** Stereotactic Radiosurgery for Patients with Recurrent Primary Central Nervous System Lymphoma

**Indication:** Recurrent or Progressive Primary Central Nervous System Lymphoma (PCNSL)

**Objectives:**

**Primary Objective:**

To assess the efficacy of stereotactic radiosurgery (SRS) by local control and overall survival in patients with recurrent or progressive PCNSL following conventional management with surgery/biopsy, fractionated radiation therapy, and chemotherapy.

**Secondary Objectives:**

1. To estimate progression-free and overall survival at 6 months
2. To evaluate the CNS toxicity of combined treatment, as measured by RTOG/EORTC Acute Radiation Morbidity Scoring and the NCI CTCAE v4.0 for late toxicity. Unacceptable toxicity will be considered to be irreversible grade 3 (severe), any grade 4 (life threatening) or grade 5 (fatal) RTOG CNS toxicity occurring within 3 months of GK.
3. To evaluate whether SRS improves tumor response or reduces the toxicity of boost radiotherapy (local or whole brain) compared to historical outcomes.
4. To evaluate quality of life of SRS
5. To evaluate the potential value of MRI diffusion weighted imaging in identifying tumor cellularity and treatment response before and after SRS.

**Study Type:** Non-Interventional

**Study Design:** Retrospective chart review

**Endpoint Classification:** Safety/Efficacy Study

Consent: Waiver of authorization/consent will be obtained

**Criteria and Justification for the Waiver with Risks and Benefits**

Risks: The potential for risks associated with this study are minimal. We will ensure that the risk to the privacy of the involved subjects remains minimal. We hereby provide our assurance that any protected health information recorded for the purpose of this research study will not be used by or disclosed to any other person or entity, except as required by law or for authorized oversight of the research study.
Benefits: No additional tests are planned as a part of this study. Information learned from our studies could benefit the patient if used in their ongoing care.

**Subject Numbers:** This is a study involving retrospective data obtained from patients with recurrent or progressive Primary Central Nervous System Lymphoma (PCNSL). We estimate a total review of 100 subjects’ charts with recurrent or progressive PCNSL. We will collect existing clinical data from approximately 40 charts.

**Summary of Patient Eligibility Criteria**
Histological confirmation of PCNSL; prior first-line treatment with surgery/biopsy, fractionated radiation therapy, and/or chemotherapy for PCNSL; age > 18 years; life expectancy >12 weeks; Karnofsky Performance Status ≥ 60; adequate organ function; signed patient informed consent or informed consent waiver obtained.

**Costs and Payment**
No additional tests or procedures will be performed for this retrospective studies. Thus, patients and their insurance carriers will incur no additional costs.

**Outcomes**
Primary: Overall survival (OS)
Secondary: Progression-free survival at 6 months (PFS-6) and overall survival at 6 months (OS), progression-free survival (PFS), location of recurrence, symptomatic adverse radiation effect (ARE) rate, reoperation rate, reoperation findings (estimated percentage of viable tumor vs. ARE), QOL analysis ADC map quantification of diffusion weighted MRI images of the tumor

**Project Summary in Lay Terms**
Primary central nervous system lymphoma (PCNSL) is a primary brain tumor in adults. Unfortunately, despite surgery, radiation therapy (RT) and chemotherapy, the prognosis for this disease is poor. It is our hypothesis that PCNSL is a “local” disease wherein treatment failure is due to failure to eradicate tumor cells in the pathways along which the tumor eventually spreads (the “border zone”). We hypothesize that treatment volume escalation will be successful at improving overall survival in patients with PCNSL when appropriate targeting and precision dose delivery is performed in a single treatment session. . We hypothesize that the addition of SRS to chemotherapy and/or standard fractionated radiation therapy will be an effective strategy for locally recurrent PCNSL because SRS will maximize the effects of radiation in the treated volume and potentially reduce radiation toxicity in the adjacent brain. This study will involve retrospective data obtained from patient charts with recurrent or progressive Primary Central Nervous System Lymphoma (PCNSL).
2. BACKGROUND/RATIONALE

Although primary central nervous system lymphomas (PCNSL) are rare, making up approximately 4 percent of CNS malignancies, the incidence of these tumors has slightly risen especially in the elderly population. It is unclear what has contributed to this increased incidence. However, the management of these tumors has evolved leading to improvements in both disease control and survival. Unlike other CNS malignancies, surgery does not play a role in the management of PCNSL (except for establishing the diagnosis) but rather is managed either with high dose methotrexate (MTX) based chemotherapy either alone or with consolidative whole brain radiotherapy (WBRT) with or without a partial brain boost to the tumor plus a margin. Treatment using either regimen is dependent on patient related factors such as age, performance status, and renal function. Patients with good performance status and renal function are often treated first with MTX based chemotherapy followed by WBRT, resulting in median overall survival rates as high as 8.5 years. Poorly performing patients on the other hand are managed with WBRT alone resulting in inferior rates of tumor control and survival compared to treatment with combined modality treatment.

Management was traditionally performed using whole brain radiotherapy, resulting in poor treatment outcomes and low survival. Due to this, a number of trials were initiated to further define the role of radiotherapy in the management of PCNSL. In patients who cannot tolerate systemic treatment with MTX, WBRT is generally prescribed to a dose of 40-50 Gy. In the elderly population (>60 years of age), WBRT is deferred following complete response using MTX based chemotherapy, due to the high risk of neurotoxicity and negative impact of quality of life associated with combined modality treatment. Regardless, younger patients with good performance status and renal function should be aggressively managed with combined modality treatment of high dose MTX based chemotherapy followed by WBRT with cytarabine to further decrease the risk of intracranial recurrence and improve survival. While some investigators recommend up-front consolidative bone marrow transplant after high dose methotrexate based chemotherapy (Oumro A, et al. Blood 2015 Jan 7. R-MPV followed by high-dose chemotherapy with TBCC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma), not every patient is eligible for stem-cell transplant. In younger patients, the current standard treatment is high dose methotrexate based chemotherapy followed by reduced-dose whole brain radiotherapy and a tumor bed boost, while older patients receive either chemotherapy (if tolerated) or radiotherapy.

Although survival has improved following the introduction of MTX treatment, local recurrence remains an issue in this population with 35-60% of patients relapsing following first line treatment. Treatment in the recurrent or salvage setting is performed without a recognized standard paradigm resulting in treatment heterogeneity. Treatment includes salvage...
chemotherapies with different agents avoiding cross-resistance, radiotherapy, radiosurgery, and stem cell transplantation ( 8, Choi, 2013 #9, 10, 11, 11). These reported salvage techniques are generally retrospective single-institution experiences, addressing the need for standardized regimens established through prospective trials or derived from large multi-institutional experiences.

The role of radiosurgery in the management of PCNSL is limited to retrospective studies or case series 12, 13, 14. The largest case series reviewed 44 patients who had diagnosis of PCNSL and were treated upfront with Gamma Knife Radiosurgery. Patients had symptomatic improvement following treatment, with improvement in performance status from (40 to 90%). 38/44 patients were in complete remission, and median survival time was 26.5 months 13. Another series in 9 patients who developed recurrent PCNSL underwent salvage linac-based stereotactic radiosurgery following initial treatment with external beam radiation. Prescribed dose was a median of 12 Gy, with the majority of patients 7/9 undergoing concurrent systemic therapy. Target volume was a median of 3.5 ml, and overall response was seen in 13/15 treated lesions (complete or partial response), with a 1 year overall survival and relapse-free survival rate of 58% and 22%. Symptomatic relief was likewise seen in the majority of treated patients (6/9), with rapid tumor response at a median of 3 days, and resulting in low toxicity (no grade 2 or greater toxicity was seen) 12. Another series involving 7 pre-treated (prior chemotherapy and external beam radiation) patients treated with radiosurgery for recurrent PCNSL prescribed to a median dose of 15.5 Gy to a median tumor volume of 6.7 ml, resulted in tumor regression in 79% of patients and a median survival of 472 days. Treatment with radiosurgery was also found to be feasible in patients with AIDS 14. These series demonstrate safety and efficacy of using radiosurgery to salvage or palliate low volume disease following initial treatment with chemotherapy, WBRT or chemotherapy followed by WBRT. This is especially important in light of the favorable therapeutic ratio that is possible this modality, resulting in a lowered risk of treatment related neurotoxicity. These initial results appear promising with the possibility of symptomatic improvement as well as prolonged PFS and OS and warrant further investigation.

3. STUDY DESIGN AND ELIGIBILITY CRITERIA

3.1 Study Design

This will be a retrospective chart review of patients with recurrent or progressive Primary Central Nervous System Lymphoma (PCNSL). All centers of the International Gamma Knife Research Foundation will provide their own IRB approval for de-identified data sharing. We will not be sharing our data externally. Other centers will only send us de-identified data from their charts. No center will see anyone else’s PHI.

3.2 Inclusion Criteria

1) Histologically confirmed PCNSL
2) Prior first-line treatment with surgery or biopsy followed by fractionated radiotherapy and/or chemotherapy is required. Additional prior chemotherapy is allowed, without limitation on number of recurrences.

3) An interval of ≥ 2 months since completion of fractionated radiotherapy.

4) Age > 18 years

5) Life expectancy of at least 12 weeks.

6) Karnofsky Performance Status score (KPS) of ≥ 60 (Appendix 1).

7) Documented recurrent disease: Recurrent disease is defined either as radiological confirmation of the tumor, as an increase in tumor size of at least 25% based upon serial MR images, or as development of a new site of disease.
   - Tumor volume will be calculated using the sum of the largest cross-sectional perpendicular diameters of contrast-enhancing tumor, the sum of the largest cross-sectional perpendicular diameters of FLAIR abnormality, or as worsened spectroscopic characteristics for any tumor type (development of ≥ 2 new voxels with CNI ≥ 3, or ≥ 25% increase in the sum of the CNI ratios within a group of previously abnormal voxels [where abnormal is defined as CNI ≥ 3]).
   - Disease must be evaluable, but does not need to be measurable.
   - The target site for SRS does not need to be located in a previously-irradiated area.

8) Eligibility for stereotactic radiosurgery using MRI targeting: The decision to treat with stereotactic radiosurgery made by a consensus of the radiation oncology, neurosurgery and medical oncology/neuro-oncology clinicians.

9) BUN < 25 and Cr < 1.7

10) Adequate bone marrow, hepatic and renal function (ANC ≥ 1,500/μL, hemoglobin of ≥ 10.0 g/dL, platelet count of ≥ 100,000/L, aspartate aminotransferase/alanine aminotransferase of ≤ 2.5 × upper limit of normal, serum bilirubin of ≤ 1.5 × upper limit of normal, urine protein creatinine ratio as determined by urinalysis of < 0.5 (for urine protein creatinine ratio of > 0.5, 24-h urine protein must have been < 1 gram), and serum creatinine of ≤ 1.5 × upper limit of normal).

3.3 Exclusion Criteria
1) Unconfirmed PCNSL
2) < 18 years of age
3) Life expectancy < 12 weeks

4. STATISTICAL CONSIDERATIONS

The initial study is a retrospective chart review with descriptive statistics. Based on these results, our goal is to develop a prospective study that utilizes radiotherapy and radiosurgery to improve outcomes.

Only authorized persons will have access to the required data. At no time during the process of data recording will subject identifiers be associated with research data. All data will be kept on a de-identified spread sheet on an NYU server. We will not be sharing our data externally.
5. Data Handling & Confidentiality:

The protected health information collected for the purpose of this research study will be assigned a unique study number and any obvious patient identifiers (name, social security number, hospital record number) will be removed from this information. Both the anonymized health information and the information linking the research code numbers to the patients’ identities will be stored in a secure manner (e.g., locked file cabinet, password protected database) accessible only to the research study investigators who are also involved directly in the health care of the respective patients. We will keep a master code list where the identifiers are linked to a subject code. The information linking the master code numbers to the patients’ identities will be stored separate from the anonymized health information. All data will be kept on a de-identified spread sheet on an NYU server and will not be shared externally. Other centers will only send us de-identified data. All information shared with us will be done in an anonymous manner.

7. Qualifications of Principal Investigator

Douglas Kondziolka, M.D.
Professor of Neurological Surgery
Has practiced neurosurgery and radiosurgery for over 24 years, and has published over 430 articles in peer-reviewed journals.

8. REFERENCES