Submission for RTOG study protocol:

"Up-Front Radiosurgical 'Leading Edge' Boost Radiosurgery for Newly Diagnosed Glioblastoma Multiforme"

Principal Investigators: Christopher Duma, MD, Minesh Mehta, MD

Brief Summary:

Glioblastoma multiforme is not a surgically curable lesion. The local control of the disease however has been improved markedly using improved microneurosurgical technique and image-guided surgery. Indeed, the extent of resection of the initial lesion correlates with survival.[4,8] In addition, volume of locally recurrent disease correlates inversely with survival.[6] It has long been known that local recurrence of glioblastoma multiforme is most commonly at the margin of the resection cavity and within the first centimeter of this margin.[9] Other variants of GBM exist such as gliomatosis cerebri and tumors with heterogeneous histology, and behave differently.

The reason cure of GBM has eluded us is likely due to the inherent nature of GBM to have already traveled down white matter pathways, well away from the tumor epicenter, by the time it has been discovered. Epitomizing this is Dandy's revelation that even hemispherectomy in patients with GBM was not curative.[3] Others duplicated his effort with similar results.[1] In 1961, Masukado reported that more than 50% of untreated brain tumors had already reached the contralateral hemisphere.[7]

Research has shown that glial cells mutate over time, become polarized, develop "invadopodia," express genes that create proteins which cause breakdown of the extracellular matrix along white matter pathways, and develop actin contractility, in order to become motile. This motile behavior suggests a reappearance of the motile phenotype seen in glial cells migrating from the germinal matrix during embryonic development.[5] It is our hypothesis that GBM is a "local" disease whose treatment failure is due to neglect of the pathways along which the tumor eventually spreads (the "leading edge"). To this end, we have performed radiosurgical boosts to the tumors' leading edge using Gamma Knife technique as adjuvant therapy to conventional involved-field radiation therapy and chemotherapy.

We targeted tumor migration pathways ("leading edge," LE) using single-fraction Gamma Knife radiosurgery (GKR) in patients with *recurrent* GBM using MR-SPECT and MR FLAIR sequences for direction. Twenty patients (median age, 55.5; range: 33-76 years) were treated using LEGKR. Six patients received 2 treatments. Ninety-five percent of patients received IFXRT and 90% received temozolamide chemotherapy pre-LEGKR and failed. Five of the 20 patients (25%) had lobar tumors, 13 (65%) had tumors invading the corpus callosum, and two patients (10%) had tumors invading the thalamus. Median leading edge volume (50% isodose line) for the two groups was 30 cc. Median dose was 11 Gy at the 50% isodose line.

Median follow-up was 11 mo. (range: 2-48mo.) Median projected survival was 17.4 months from diagnosis and 12.7 months from recurrence and LEGKR. One patient required admission for mannitol, three had hydrocephalus requiring a shunt. Four patients (20%) are alive more than three years after diagnosis. There were no direct radiation-

induced injuries.

In a recent study, the median survival time for patients with recurrent GBM treated with temozolomide was 8.75 months. Another study reported only a 16% response rate for recurrent GBM using temozolamide. Our results show a significant survival advantage over historic conventional treatments and temozolamide from this single session treatment.

It will be important to study this concept in a multicenter format. Volumetric maps of LE radiosurgical boost zones will be directed by FLAIR abnormality and/or MR-SPECT positivity, and will be confirmed for all patients by the principal investigators prior to actual treatment. The impact of this treatment has the most theoretical potential for early control of tumor cell migration in up-front treated patients upon initial diagnosis. A large number of patients may be accumulated quickly with a multicenter format, and because of the high mortality of the disease, statistically significant data should become available after 12-18 months of the trial.

1. Bell E, Karnosh, LJ: Cerebral hemispherectomy. **J Neurosurg 6:**285-293, 1949
2. Brat DJ, Castellano-Sanchez AA, Hunter SB, et al: Pseudopalisades in glioblastoma are hypoxic, express extracellular matrix proteases, and are formed by an actively migrating cell population. **Cancer Res 64:**920-927, 2004
3. Dandy W: Removal of right cerebral hemisphere for certain tumors with hemiplegia. Preliminary report. **JAMA 90:**823-825, 1928
4. Daneyemez M, Gezen F, Canakci Z, et al: Radical surgery and reoperation in supratentorial malignant glial tumors. **Minim Invasive Neurosurg 41:**209-213, 1998
5. Demuth T, Berens ME: Molecular mechanisms of glioma cell migration and invasion. **J Neurooncol 70:**217-228, 2004
6. Keles GE, Lamborn KR, Chang SM, et al: Volume of residual disease as a predictor of outcome in adult patients with recurrent supratentorial glioblastomas multiforme who are undergoing chemotherapy. **J Neurosurg 100:**41-46, 2004
7. Masukado YMC, Kernohan, J. W.: The Growth of Glioblastoma Multiforme (Astrocytoma Grades 3 and 4) in Neurosurgical Practice. **J. Neurosurg 18:**636-644, 1961
8. Nitta T, Sato K: Prognostic implications of the extent of surgical resection in patients with intracranial malignant gliomas. **Cancer 75:**2727-2731, 1995
9. Wallner KE, Galicich JH, Krol G, et al: Patterns of failure following treatment for glioblastoma multiforme and anaplastic astrocytoma. **Int J Radiat Oncol Biol Phys 16:**1405-1409, 1989