Abstract—The primary goal was to determine if fast neutron radiotherapy (FNRT) followed by photon boost would increase survival in patients with glioblastoma. A secondary objective was to use 18F-Fluoromisonidazole Positron Emission Tomography (18F-MISO PET) to detect changes in tumor/tumor bed hypoxia. Eleven patients with glioblastoma were accrued. Ten patients were included in the analysis and received 15 Neutron-Gray (N-Gy) in tri-weekly 1 N-Gy fractions followed by 14.4 Gy photon boost using daily 1.8 Gy fractions. Three patients had 18F-MISO PET prior to and at least once after 4 weeks of FNRT. Median follow-up was 8 months (range 2 to 14). Median age was 51 years (range 39 to 67) and median Karnofsky Performance Status at the start of treatment 70 (range 60 to 90). Median time to progression was 5 months and median survival 10.5 months. At last follow-up in January 2003, 9 patients had progressed and 6 had died of progressive disease. The incidence of neurotoxicity seen in this protocol was worse than that seen in standard brain radiotherapy without the benefit of increased survival or local control. 18F-MISO PET did not show a significant decrease in hypoxic volume that is well known to be a radiation resistant within the tumor after four weeks of FNRT.

Index Terms—18F-Fluoromisonidazole Positron Emission Tomography, Glioblastoma, Hypoxia, Neutrons, Radiation therapy

I. INTRODUCTION

Glioblastoma multiforme (GBM) is a primary brain malignancy that classically has been hard to manage, with poor survival rates and outcomes with photon radiotherapy using standard fractionation with an alkylating agent. Previous studies have demonstrated that irradiation of the brain leads to areas of post-irradiation necrosis [1]. The recurrence rate, regardless of method of treatment, is predominantly local, with little, if any, propensity to spread outside of the brain [2], thereby providing impetus to irradiate areas of residual disease and the tumor bed rather than the entire brain [3].

A potential problem with these tumors is that there are areas of hypoxia that standard photon radiotherapy fails to address [4]. Thereby, the hypoxic fraction may be corollary to the success of treatment, as if oxygen cannot enter these cells, larger molecules, such as chemotherapeutic drugs, may not be able to enter [5,6].

The objective of this study was to use fast neutron radiotherapy (FNRT) to improve the hypoxic index of GBM tumors. This was followed by conventional photon therapy as a boost to those areas rendered better oxygenated by the neutrons. Fast neutrons have been used in the past to re-oxygenate previously hypoxic tumors [7,8]. Other studies have looked at GBM along with dose escalation and fractionation schemes that offer promise to treating the brain with fast neutrons [9-13]. The secondary objective was to demonstrate the extent of the effect of neutrons on tumor hypoxia, which can be measured using 18F-Fluoromisonidazole Positron Emission Tomography (18F-MISO PET), as previously determined in in-vivo studies [5,14]. This report therefore deals with the final findings of survival benefit and toxicities generated from this prospective trial.

II. MATERIALS AND METHODS

From July 2001 to January 2002, 11 patients, 10 of whom were analyzable, were accrued to this prospective trial.

A. Eligibility

Eligibility for study inclusion consisted of diagnosis of GBM or grade IV astrocytoma or gliosarcoma, at least 18 years of age, hemoglobin ≥ 10q/dL, absolute neutrophil count ≥ 1500/microliter, and platelet count ≥ 100,000/microliter. The patients could not have any other medical illnesses contraindicative of radiation and had a Karnofsky Performance Status (KPS) ≥ 60. Also, no prior radiation or chemotherapy
was allowed, and women must not be pregnant. Women of childbearing age must have been on birth control.

Pretreatment data collection included history and physical, KPS, disease assessment, toxicity notation, and radiation oncology evaluation. Also, pretreatment baseline laboratory values, such as complete blood count, differential, and serum creatinine were assessed. Magnetic resonance imaging (MRI) of the brain, pretreatment, was also obtained, and \(^{18}\)F-Fluoromisonidazole Positron Emission Tomography (\(^{18}\)F-MISO PET) scans were done on patients who agreed to the imaging study.

**B. Treatment**

Target volumes for fast neutron therapy were designed to encompass the gross tumor volume, including hypoxic areas, as well as surrounding microscopic disease and were delineated from preoperative T2 signal enhancement on MRI, plus a 2.0 cm margin. Treatment with fast neutrons was given in 1 N-Gy fractions over five weeks (3 fractions/week) for a total dose of 15 N-Gy. The photon boost target volumes were designed to boost areas of gross tumor volume, presumed reoxygenated by the delivery of neutrons, and were determined by postoperative T1 signal enhancement on MRI with a 2.5 cm margin. The boost was given to 14.4 Gy with standard fractionation of 1.8 Gy fractions for 1.5 weeks. One patient received 12 N-Gy at 1 N-Gy per fraction followed by a photon boost of 18 Gy using 1.8 Gy fractions. Isodose conformity was achieved to the planning target volume using non-coplanar fields where appropriate. Blocking was achieved for the optic nerves and chiasm to keep total neutron dose below 12 Gy ipsilaterally and 9 Gy contralaterally. Mid brain and brain stem blocking were also achieved as necessary to keep total dose to these structures below 12 Gy. The optic chiasm was blocked from the photon boost field. Radiation doses were prescribed to the isocenter, and a multileaf collimator was used for field shaping. Treatment was delivered via the University at Washington Medical Center (UWMC) fast neutron facility.

**C. Supportive Treatment**

Anticonvulsants were administered as necessary for the patient population. Dexamethasone (4 mg qid) was administered two days prior to the beginning of radiation and was tapered after the cessation of fast neutron treatment if possible. No chemotherapy was used for initial definitive treatment. Three of the patients had \(^{18}\)F-MISO PET scans once prior to and at least once after 4 weeks of fast neutron radiotherapy.

**D. Evaluation**

The patients were evaluated based on KPS, neurotoxicity, and dexamethasone dose during and after treatment. All patients were to be consulted every 3 months for the first year, every 4 months for the second year, and every 6 months for the third through fifth years until disease progression and every year thereafter until death.

**E. Statistical Consideration**

The endpoint for the study was survival outcome and changes in hypoxic volumes of the tumor or residual tumor bed. Recurrences were noted, and treatment effects were also followed through follow up and were recorded to assess the benefits or detriments of neurotoxicity.
III. RESULTS

A. Population Characteristics

From 7/2001 to 1/2002, 11 patients with primary GBM received fast neutron therapy followed by a photon boost. One patient was excluded from the trial, as the course of treatment was not completed due to the stopping rule being invoked by the data monitoring and safety board closing the protocol. Of the 10 patients who completed the study, two of the patients had only biopsies, four had subtotal resection, and four had gross total resection. The patients were evaluated based on KPS, neurotoxicity, and dexamethasone dose during and after treatment. There were 5 males and 5 females treated to protocol completion. Evaluation of 8 patients followed specifically during treatment was also used for analysis. The median age of onset of the 10 patients evaluated was 51 years (range 39 to 67). The median tumor volume was 71.19 cm$^3$ (range 6.63 to 124.80), along with a median KPS pre-treatment of 70 (range 60-90). The median time from date of diagnosis to date of initiation of treatment was 35 days (range 12-50). Data for initial tumor size and location can be found in Table 1.

B. Complications of Treatment

Of 8 patients specifically followed during treatment, 5 experienced fatigue and 5 experienced headaches. Five patients also experienced erythema at the radiation site during treatment. By week 7 of treatment, the average KPS had fallen below 70 (Fig. 1). As of week 5 of treatment, each patient had experienced at least one grade 1 neurotoxicity. Seven of the 10 patients experienced grade 3 fatigue or somnolence post treatment. Lower extremity weakness was also present in 3 of the 10 patients post treatment. Incidence of grade three neurotoxicity was greatest in the first and third months post treatment (Fig. 2). KPS fluctuated over the months post treatment, attributed to a decreased patient pool as time and disease progressed. The average KPS for the first six months post treatment was 60 (range 40 to 90), with a survival rate of 80% at the end of this period (Fig. 3). Dexamethasone dose peaked at the end of treatment and was gradually decreased post treatment as patient tolerance allowed.

C. Survival

Interestingly, patients who had a pretreatment KPS that was higher had a worse survival rate than those who had a lower KPS at presentation (Fig. 4). Also, there was a correlation between advanced age and decreased survival (Fig. 5). There was no correlation noted between extent of resection and survival.

As of January 2003, 9 of the 10 patients had progressed. All six of the patients who have died did so due to progressive disease. Time to tumor progression was defined as the date of tissue diagnosis to date of tumor progression. Survival was defined as date of tissue diagnosis to date of death. Progression of disease was defined as a post treatment increase in size of the enhanced tumor volume or new enhanced lesions in the brain on MRI or PET scans, and/or progressive neurological symptoms directly attributable to increased tumor growth. Median time to progression (TTP) was 5 months. Median survival time from diagnosis was 10.5 months.

IV. DISCUSSION

In summary, this study attempted to demonstrate the benefits of fast neutron therapy followed by a photon boost for patients with glioblastoma multiforme. However, survival time was
about the same as conventional photon therapy alone. In addition there was increased neurotoxicity and a decrease in the patients’ quality of life as compared to a previous mixed neutron/photon study [11]. On the other hand these findings were consistent with those of Parker, et al., which included previous work done with fast neutrons and whole brain irradiation, demonstrating radiation necrosis and extensive neoplastic infiltration on autopsy [9]. A likely reason for failure of radiation with fast neutrons followed by a photon boost was the drawn out nature of our treatment protocol allowing for tumor repopulation. This effect may have outweighed any benefit in improved oxygenation we may have obtained from the use of the neutrons.

All patients except one finished the prescribed radiation dose. The one that did not was due to the termination of the trial when the stopping rule was invoked by the data monitoring and safety board due to the adverse toxicity seen during the trial on the other patients. This demonstrates that despite the neurotoxicities, which did not go above grade 2 for the duration of treatment, the patients were able to tolerate treatment rather well. Grade 3 toxicities only began post treatment, demonstrating delay in subacute effects with evidence of gliosis and edema on limited autopsy data.

Based on neurotoxicity data generated in this study, it is possible to compare the neurotoxicity with other studies that have used conventional therapy. Chang, et al., published a study on postoperative radiotherapy and chemotherapy that is more corollary to standard treatment [15]. Sole radiotherapy arms in the study included a control radiation dose of 6000 rad/6-7 weeks (whole brain), and control plus boost of 1000 rad/1-2 weeks to the tumor. Additional arms of the study included one with control radiation plus BCNU, as well as one with BCNU and DTIC.

The median survival seen in this cohort, 10.5 months, was consistent with the median survival seen in other radiotherapy only protocols [16] but lower than that seen in more recent trials of chemoradiation using Temozolomide, 14.6 months [17].

A potential problem with comparison of this study pool is its limited size and therefore decreased power or inference rate. However, due to the vast neurotoxicities as delineated above, it is imperative to note that additional neurotoxicities without survival benefit were not acceptable and warranted study termination.

Death in all patients (6 out of 10 as of January, 2003) was due to recurrence or progression of tumor. This correlates with the inability of fast neutrons to achieve the goal demonstrated in other tissue types, again to re-oxygenate the tumor.

Future work is necessary to better define hypoxia in tumor both pre- and post-treatment. While fast neutrons may be a viable option in other sites of disease, their usefulness in primary brain malignancies remains in question.

REFERENCES