Hypofractionated Stereotactic Radiotherapy As Salvage Therapy For Recurrent Low-Grade Glioma

Research Article

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Summary

Previous studies have reported encouraging survival results and favorable toxicity data with stereotactic radiation therapy (SRT) for patients with recurrent gliomas. We sought to determine the efficacy and tolerability of hypofractionated-SRT (H-SRT) in patients presenting with recurrent low-grade gliomas and the role of chemotherapy combined with radiation therapy in this patient population.

I. Introduction

Low-grade gliomas (LGG) consisting of World Health Organization (WHO) grade I or II tumors represent 10% of all newly diagnosed primary brain tumor (Jemal et al, 2006; Central Brain Tumor Registry of the United States, 2005). Primary treatment consists of surgery and radiation therapy with an undefined role for chemotherapy. The precise time to deliver radiation therapy following surgery at initial diagnosis is unclear and randomized studies have failed to demonstrate a survival advantage in patients receiving radiation therapy immediately following surgery or at progression. Radiation has been routinely administered for tumors with a threshold growth potential quantified by a Ki-67 labeling index (McKeever et al, 1998; Schiffer et al, 1997).

Recurrence of low-grade gliomas represents a treatment challenge, as there is currently no standard of care. Many surgeons are reluctant to offer salvage resections as complete resection is often limited secondary to the infiltrative nature of the tumors (Dirks et al, 1993; Harsh, 1987). Chemotherapy may be beneficial in patients with oligodendroglioma but its role in low-grade astrocytoma is less clear (Eyre et al, 1993; Van Den Bent et al, 2003; Van Den Bent et al, 2003; Jaeckle et al 2003; Buckner, 2003). Previous studies have reported encouraging survival and toxicity with stereotactic radiation therapy (SRT) for patients with progressive high-grade glioma following standard therapy and there is evidence that this treatment may be beneficial in low grade gliomas as well (Combs et al, 2005). Fractionated therapy is advantageous in treating recurrent previously irradiated brain tissue particularly when located in eloquent areas, as it takes advantage of the precision of radiosurgery but with less toxicity as a result of delivering the dose over many fractions. Treating with multiple fractions of radiation therapy does require weeks of treatment, which represents an inconvenience for the patient.

Hypofractionated-stereotactic radiation therapy (H-SRT) utilizes these principles but is able to shorten the number of weeks of treatment. This is not only more beneficial to patients with recurrent gliomas with respect to quality of life and convenience but also may represent a decrease in cost associated with re-treatment. Literature is sparse regarding the toxicity or efficacy of hypofractionated stereotactic radiotherapy. In addition, it is unclear what role systemic agents play when combined with radiation in the treatment of recurrent low grade gliomas.
We therefore sought to determine the efficacy and tolerability of H-SRT in patients presenting with recurrent low-grade gliomas following standard therapy. To our knowledge this is the largest cohort of low-grade patients treated with H-SRT for recurrent disease and one of the few reports to describe the combination of chemotherapy and re-irradiation for low-grade gliomas.

II. Materials and methods

A. Patient Population

Between 1994 and 2008, 22 patients with clinical and radiographic imaging evidence of low-grade glioma progression following initial treatment were treated with (H-SRT). This study was approved by the Thomas Jefferson University Cancer Center Institutional Review Board (IRB) prior to patient chart review. At time of recurrence, a multidisciplinary team consisting of a radiation oncologist, a neurosurgeon and a neuro-oncologist evaluated all patients.

All patients were initially diagnosed with WHO grade II tumors and received fractionated external beam radiation with a median dose of 59.4 Gy based on histopathologic diagnosis which included quantization of a Ki-67 labeling index of > 5% per 400x field. While not part of the WHO grading system, an increased Ki-67 labeling index is a marker for increased mitotic activity and has demonstrated an association with increased tumor aggressiveness. Ki-67 is an IgG1 class monoclonal antibody and is recognized as a core antigen present in proliferating cells and absent in quiescent cells. The precise function of the Ki-67 protein is still unclear however; higher levels are associated with increased malignant potential and have demonstrated prognostic significance.

While no standard of care exists regarding the decision to irradiate low grade gliomas as part of the initial treatment, it is our institutions policy is to treat patients with radiation if they exhibit an increased Ki-67 labeling index.

The initial histological diagnosis was astrocytoma in 18 patients and oligodendroglioma in 4 patients. Median age at primary diagnosis was 38 (range 22-76 years). Upon primary diagnosis of the tumor 18 patients had a subtotal resection, 1 patient had a total resection and 3 patients underwent biopsy only. Median age at recurrence was 44 years (range 26-77 years). The median treatment volume was 26 cc (range 1.2cc to 96 cc).

Twelve of the 22 patients had a surgical resection prior to re-irradiation for tumor recurrence. With prior irradiation our pathologists will not grade recurrent tumors according to WHO criteria. However, the pathology reports indicated the majority of these patients had undergone some transformation. The majority of patients demonstrated a Karnofsky performance score of greater than 80 with 4 patients exhibiting scores of 70 or less. The median interval from completion of initial radiotherapy to the start of re-irradiation was 31 months (range 1 to 184 months). Nine patients received chemotherapy at initial diagnosis consisting of procarbazine, CCNU and vincristine (1), BCNU (3), temozolomide (3), cisplatinum (1), and vinblastine and methotrexate (1). Only one of the four oligodendrogliomas received chemotherapy at initial diagnosis. Nine of the 22 patients received chemotherapy at recurrence with H-SRT of which temozolomide was the most common regimen (7). One patient received procarbazine and one patient received Sunitinib with H-SRT.

Patients underwent bimonthly clinical examinations with at least one physician from the initial team of radiation oncologists, neurosurgeons and neuro-oncologists. If clinical deterioration prevented a visit to a physician of the initial team, primary care physicians were contacted for follow-up information. Clinical response was determined by the presence of neurological improvement or a decrease in steroid dose without clinical neurologic deterioration. Steroids were prescribed during re-irradiation if clinically indicated.

B. Treatment Planning and Delivery

Patients were fitted with the Gill-Thomas-Cosman (GTC) relocatable frame (Laing et al, 1993). After the GTC frame was fitted, the patient was taken to the MRI and/or CT scanning suite where the Brown-Roberts-Wells (BRW) fiducial cage was placed on the GTC frame and transaxial images were obtained. Prior to June 2004, treatment planning was carried out with the X-Knife 3-D planning system (Radionics, Burlington, MA), which used 6 MV photons delivered stereotactically with a dedicated 600SR linear accelerator (Varian Corporation, Palo Alto, CA). After June 2004, treatment planning was carried out with Brain Lab (Novalis). With mMLC leaves and an Exac Trac feature.

Gross tumor volume (GTV) was defined by the gadolinium-enhanced tumor edge on a T1 weighted series. The PTV was considered equivalent to the GTV and edema was not included in the treatment volume. Tumors were treated to the 85-90% isodose line and coverage of the target volume was reviewed on the planning system. H-SRT was delivered using daily fractions of 3.5 Gy. Total doses ranged from 24.0 – 45.0 Gy with a median dose of 35 Gy.

C. Study Endpoints

The primary endpoint of the study was median survival time (MST) measured from the date of initiation of re-irradiation. Other endpoints included progression-free survival, overall survival, neurological, clinical, and radiographic responses, as well as frequency of patients developing unacceptable (≥ grade 3) acute or delayed CNS toxicities (scored by RTOG criteria). CNS toxicity was defined as the development of any new neurologic symptoms following radiation that were felt to be attributable to the treatment. Progression free survival was calculated from the first day of re-irradiation treatment until tumor progression or death (whichever happened first) using the Kaplan-Meier method. All patients were diagnosed with recurrence based on radiographic presence of tumor progression on MRI. All 22 patients were followed with MRI scans which were obtained 6 - 8 weeks after H-SRT and at three-month intervals thereafter. Response was determined as defined by MacDonald et al.

III. Results

MST from date of diagnosis was 72.5 months (range 10-192 mo). MST from re-irradiation was 8.5 months (range 2-66 months; Figure 1).

Median progression free survival time from H-SRT was 5 months (range 1-46 months; Figure 2).

At six-week follow-up, 11 patients (50%) experienced clinical improvement following H-SRT as indicated by either decrease in steroid dose or improvement in neurologic symptoms. Specifically, steroid dose reduction was considered a result of re-irradiation if patients were taking steroids prior to treatment and were able to reduce the dose following treatment.
No patients demonstrated clinically significant acute morbidity, and all patients were able to complete the prescribed radiation dose. No patient required hospitalization or surgery for early acute or delayed toxicity. MST from diagnosis in patients receiving chemotherapy with H-SRT was 127 months compared to 30.5 months in patients receiving re-irradiation only. Median survival from H-SRT was 17 months for patients receiving chemotherapy with H-SRT and 7 months for patients receiving H-SRT only \((P = 0.02; \text{Figure 3})\).

Of the four patients with oligodendroglioma, 3 received chemotherapy. In this group, the MST from re-irradiation was 32 months (46, 47 and 2 months) vs. 20 months in the patient who did not receive chemotherapy with re-irradiation. Of note, the patient who survived only two months following H-SRT had been diagnosed 10 years prior to H-SRT and had two previous recurrences, which had been treated with resection and chemotherapy. The MST of patients with low grade anaplastic astrocytoma was 5.5 months in patients who did not receive chemotherapy with re-irradiation vs. 14 months in patients who received concomitant systemic chemotherapy \((P = 0.04)\).
IV. Discussion

Recurrence of low-grade gliomas represents a treatment challenge, as there is currently no standard of care. While there is evidence to suggest that radiation is effective following resection at initial diagnosis in the presence if increased Ki-67, the role of radiation at recurrence is vague. Salvage resections often are not feasible and are limited by the infiltrative nature and location of the tumors (Dirks et al, 1993; Harsh, 1987). Other options at salvage include re-irradiation, chemotherapy or a combination of the two modalities. While the goal of therapy is remission, the prognosis in the majority of these patients is grim and, therefore, assessment of the toxicity associated with therapy is critical as toxic therapy can be detrimental to patient quality of life.

Critical review of the literature pertinent to low-grade gliomas is challenging as many studies analyze low and high-grade patients together. The heterogeneity of tumors within the low-grade cohort further complicates interpretation as median 5-year survival of patients ranges from 37% (astrocytomas) to 70% in patients with oligodendrogliomas (Brandes et al, 2003). In addition to these inherent survival differences, different histologies have different responses to adjuvant therapy. Furthermore, there is currently no standard regarding the timing of various salvage modalities. For example the first course of radiation therapy may be offered as treatment at initial diagnosis or at first or second recurrence making literature examining survival times from re-irradiation difficult to decipher.

The role of salvage chemotherapy is unclear. Efficacy has been demonstrated in patients with oligodendroglioma but the role in low-grade astrocytoma is not established (Eyre et al, 1993; Van Den Bent et al, 2003; Van Den Bent et al, 2003; Jaeckle et al, 2003; Buckner, 2003). Oligodendrogliomas have demonstrated responses to procarbazine, lomustine and vincristine (PCV) (Cairncross et al, 1994; Paleologos et al, 1999). Temozolomide alone for recurrence has demonstrated promising results and is an attractive option as it is less limited by cumulative toxicity (Quinn et al, 2003). A large phase II trial of temozolomide in patients with anaplastic astrocytoma and anaplastic oligoastrocytoma by Yung et al found a median survival time from start of salvage therapy of 14.5 months (Yung et al, 1999). Of note, they did not report a survival difference between anaplastic astrocytoma and anaplastic oligoastrocytoma, indicating temozolomide may have some success in treating the traditionally less chemosensitive anaplastic astrocytomas.

Previous studies have reported encouraging survival results and favorable toxicity data with SRT for patients with progressive high-grade glioma following standard therapy and there is evidence that fractionated stereotactic re-irradiation therapy results in increased survival in recurrent LGG with few side effects (Combs et al, 2005). Fractionated therapy is advantageous in treating previously irradiated brain tissue particularly when located in eloquent areas as it takes advantage of the precision of radiosurgery but, in delivering the dose over many fractions, decreases toxicity. Treating with multiple fractions of radiation therapy does require weeks of treatment, which represents an inconvenience for the patient.

Coombs et al examined the effectiveness of re-irradiation in patients with recurrent low-grade recurrences using 2 Gy fractions delivered to a median dose of 36 Gy (Combs et al, 2005). They found re-irradiation was tolerated by all patients with minimal side effects and resulted in a MST of 111 months with MST from re-irradiation of 23 months. In our study the MST from re-irradiation was significantly lower (9 months). There are several differences in our patient populations, which may explain this discrepancy. Our patient population was older with an average age of 46 vs. 41 in the Coombs study (with over 68% of patients under age 40). In addition, the majority of patients in their study (92%) had a KPS of >70% while only 17 patients (77%) in our cohort had a KPS of 70 or less which reflects our institutions policy to aggressively treat recurrent gliomas. Finally, the MST in their study was 111 months with a median time between initial irradiation and re-irradiation of 50 months. In contrast we report a MST of 12.5 months with a 31-month interval between initial irradiation and re-irradiation, indicating other factors such as tumor aggressiveness may have impacted the results.

While the role of chemotherapy combined with radiation therapy has been well established for patients with newly diagnosed glioblastoma multiforme (Stupp et al, 2005; Combs et al, 2005), there is a paucity of data reporting on the combination of chemotherapy and radiation therapy for recurrent gliomas and the majority of studies have examined this combination in high-grade gliomas (Lederman et al, 2000; Aricase et al, 1999; Glass et al, 1997). A recent study by Coombs et al examined the combination of temozolomide with fractionated re-irradiation in 25 patients with recurrent gliomas of which 7 presented with low-grade histology (Combs et al, 2008). The treatment was well tolerated and they found an overall survival from re-treatment of 8 months with 6 and 12-month survival of 81% and 25% respectively. While they did not report specifically on survival within the low-grade cohort, histological classification did not contribute to overall survival on multivariate analysis. It is difficult to extrapolate their results to our group of patients given the small number of low-grade patients in their study however; we report a significant difference between patients who received chemotherapy with adjuvant H-SRT and those who did not. These differences could not be accounted for by other factors such as age, KPS or histological diagnosis.

Literature is sparse regarding the toxicity or efficacy of H-SRT in the setting of progressive gliomas. H-SRT takes advantage of the stereotactic precision as well as the properties of a standard fractionation schedule but is able to shorten the number of weeks of treatment. This is not only more beneficial to patients with recurrent GBM with respect to quality of life and convenience but also represents a decrease in cost associated with re-treatment.
The Royal Marsden experience reported on 36 glioma patients treated at the time of recurrence (Laing et al, 1993; Shepherd et al, 1997). Total dose was escalated incrementally from 20-50 Gy in 5 Gy fractions. A 34% actuarial risk of developing presumed delayed radiation complications was reported. Stereotactic radiotherapy doses >40 Gy significantly predicted for radiation toxicity with two patients (6%) requiring re-operation due to toxicity.

VanderSpek et al conducted a phase I dose escalation study with a hypofractionated regimen ranging from 20-50 Gy in 5 Gy fractions combined with a cisplatin in 9 patients and found that 30 Gy in 6 fractions combined with low dose cisplatin was well tolerated with minimal acute toxicities but did cause late radiation necrosis (VanderSpek et al, 2008). Glass et al examined the combination of external beam radiotherapy and weekly cisplatin for recurrent malignant astrocytoma (Glass et al, 1997). Radiation therapy was delivered once or twice weekly with a majority of patients receiving 42 Gy in 6 Gy fractions. Late effects included otoxicity (3 patients) and radiation necrosis in 3 of the 20 patients. Both studies involved high-grade patient’s with poor prognosis making assessment of long-term toxicity difficult.

Of note, these studies used 5 to 6 Gy fractions, which are larger than the 3.5 Gy fractions used in our patient population. Certainly, higher doses per fraction are noted to be associated with increased long-term toxicity in late responding tissue in other disease sites. While this is less relevant in a population with such poor prognosis, within the low-grade glioma population, this should be taken into consideration.

Our study is limited both by its retrospective nature and small number of patients. It is, however, the largest study to report on the efficacy and tolerability of H-SRT in patients initially diagnosed with low-grade gliomas and supports previous results indicating a possible advantage to combining chemotherapy with irradiation for recurrent low-grade gliomas.

It is difficult to compare our findings to other studies given the heterogeneity of the tumors and of the variety and timing of treatment options. With glioblastoma multiforme patients, most patients have undergone a standard initial treatment regimen of resection followed by radiotherapy with concomitant chemotherapy. In low-grade gliomas, many patients are treated with resection alone and may receive radiation therapy only at first recurrence. In many of the studies examining the role of chemotherapy at recurrence, few patients have received prior radiation. Combined with the heterogeneity of tumor histologies, it is difficult to make comparisons between studies.

Within our patient cohort the majority of patients with available pathology at recurrence had undergone malignant transformation. While not every patient had resection, it is likely the results of the histopathologically confirmed patients would extend to some proportion of the remaining patient population. It is interesting to note our results differ from studies looking at the effect of chemotherapy and radiation at recurrence in high-grade patients. We report survival times of 17 months from re-irradiation in patients receiving chemotherapy with compared to 7 months for patients receiving H-SRT only which is consistent with the best reported results for patients for patients of similar age and KPS. It may be that these patients are more sensitive to systemic therapy during or following transformation and thus make up a different group than those initially diagnosed with high-grade tumors.

Within these confines we have tried to report on a patient population with similar treatment histories who were successfully treated with H-SRT at recurrence with minimal toxicity. Within our patient population we were able to analyze patients who received chemotherapy with radiation therapy vs. those who did not and found a significant advantage to this combination within this small group of patients. A median dose of 35 Gy in 10 fractions when applied to the tightly defined target of enhancing tumor edge without edema is well tolerated in this patient population.

The current study represents the largest series to examine the efficacy and tolerability of H-SRT for recurrent low-grade gliomas. The low toxicity profile and evidence of symptom improvement associated with this regimen justify further evaluation. Chemotherapy or possibly biologic agents given with re-irradiation was associated with increased survival in this patient population and should be investigated in future trials.

References


Fogh et al: Re-irradiation of recurrent low-grade glioma