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Survival outcome and neurotoxicity in patients of high-grade gliomas treated with conformal radiation and temozolamide

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Abstract

Background: To study the survival outcome and neurotoxicity grades in patients of high-grade glioma (HGG) treated with conformal radiation and temozolamide. **Materials and Methods:** Forty-six patients of HGG received conformal post operative radiation and temozolamide in the period 2003 to 2007. Twenty seven patients had near total resection, 17 had subtotal resection and 2 had biopsy only. 33 patients (71.7%) were treated with IMRT and 13 (28.3%) received 3DCRT (conformal radiation). Median dose delivered to PTV2 was 61.58Gy and PTV1 was 54.3Gy. Neurotoxicity was assessed with sequential MRI and cognitive disturbance was evaluated and grading was done according to CTCAE version 2.0 and 3.0 respectively. **Results:** At a median follow-up of 12 months, median progression free and overall survival was 9 months and 15 months respectively. At 6 months, MRI neurotoxicity of grade 1, 2, and 3 was seen in 34.3, 11.4 and 2.9% patients. At 24 months, 35.3 and 29.4% patients had grade 1 and 2 neurotoxicity respectively. Cognitive disturbance was grade 0, 1, 2 and 3 in 55, 34.4, 6.8 and 3.4% patients at 6 months and grade 0 and grade 1 in 51.1 and 42.8% patients respectively at 24 months. **Conclusion:** Conformal Radiation yields low grades of MRI assessed neurotoxicity and cognitive disturbance in patients of HGG with no adverse impact on local control and survival.

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Full Text

Introduction

High-grade gliomas (HGG) usually attain a large size at the time of diagnosis which predisposes a large volume of normal brain to high dose while delivering postoperative radiation. Postoperative radiation therapy with concurrent and adjuvant temozolamide (TMZ) has become the standard of care in patients with high-grade gliomas with an improvement in progression free and overall survival. [1] Addition of chemotherapy can enhance the risk of radiation-induced neurotoxicity and is best described in patients with primary CNS lymphoma and primary brain tumors. [2],[3],[4] At present, there is very little available data regarding the incidence or severity of neurotoxicity in patients of HGG undergoing radiation with conformal radiation techniques like intensity modulated radiation therapy (IMRT) and 3D-conformal radiation therapy (3D-CRT) with concurrent administration of TMZ.

As the long-term survival for patients with HGG increases, an increase will also be certainly seen in number of patients suffering from late effects of radiation. [5] Late sequelae of radiotherapy are thought to be due to white matter damage from vascular injury, demyelination and necrosis and they tend to be irreversible and progressive. [6] It has been shown that IMRT enables the reduction of volume of normal brain receiving high dose of radiation which has obvious implications for reducing neuro-cognitive deficits in long-term survivors. [5],[7] To ensure optimal tumor coverage with minimal radiation injury, highly conformal radiotherapy techniques like IMRT and 3D-CRT were adopted at our center since April 2002.

In this report, we have prospectively evaluated neurotoxicity and cognitive dysfunction in patients of HGG who received conformal radiation and concurrent and adjuvant temozolamide. A comparison with regard to toxicity has been made with historical series where patients were treated with conventional 2D-radiation.

Materials and Methods

Forty six consecutive and unselected patients of HGG were treated at our center between July 2003 and Nov 2007. Approval was obtained from the hospital ethics committee and the study was conducted in accordance with ethical norms.

Twenty nine patients were males and 17 females with median age of 51 years (range 26 - 73 years). KPS was 70%-100% in 32 patients and <70% in 14 patients [Table 1]. Pre-operative evaluation included CECT scan (all patients) and gadolinium (Gd) enhanced MRI (42 patients). Post-operative CT scan was available in all the patients for documenting residual tumor. Post-operative MRI was done in 42 patients (91.3%) for CT-MRI fusion with T-1 weighted, T-2 weighted, fluid attenuation inversion recovery (FLAIR) sequence and T-1 contrast sequence. Histologically, 34 patients had GBM and 12 had grade 3 anaplastic astrocytoma. Extent of resection was determined by radiological studies (CT/MRI) and neurosurgical notes. {Table 1}

Treatment protocol consisted of concurrent radiation therapy (5 fractions per week) and TMZ (7 days per week) at a dose of 75 mg/m 2 . Thirty three patients (71.7%) received IMRT and thirteen patients (28.3%) were treated with 3DCRT [Table 1]. Adjuvant TMZ was started after a gap of 4-6 weeks at a dose of 150-200mg/m 2 for 5 days. Six such cycles of TMZ were given at 28 days interval.

Post operative tumor bed and residual tumor (GTV) was defined with CT-MRI fusion with T-1 weighted image. PTV2 was generated by adding 0.5 cm margin to GTV. Clinical target volume (CTV) consisted of GTV and edema visualized on T-2 weighted image with a 1.5 cm expansion all around. PTV 1 was defined by adding a 0.5 cm expansion to the CTV to account for setup uncertainties. A dose of 60Gy in 30 fractions was prescribed to PTV2 and 54Gy in 30 fractions was prescribed to PTV1.

Follow up procedures and evaluation criteria

First response and toxicity assessment was done at 1 month along with Gd-MRI. Further follow-up included monthly check-up with 2 monthly MRI in the 1 st year and 3 monthly thereafter. KPS and steroid requirement was recorded at each follow-up visit. Sixteen patients (34.7%) had one additional functional study in the form of GHA or Thallium SPECT and CT-PET

Neurotoxicity was evaluated for surviving patients at 3, 6, 12 and 24 months with the help of various sequences of MRI and grading was done according to CTC version 2.0 [Table 2]. [8] MR spectroscopy was done if there was doubt about tumor recurrence or necrosis. In case of equivocal findings regarding the presence of viable tumor versus necrosis, SPECT Thallium or GHA was performed in 12 patients and additional 4 patients had FDG CT-PET scan. Cognitive disturbance was recorded at baseline, 6 months, 12 months and 24 months following the completion of radiation therapy and grading was done according to CTCAE version 3.0 [Table 2]. [9] It was available in 29 patients since 15 patients died within 6 months and 2 patients were not evaluable. {Table 2}

Statistical analysis

Progression free and overall survival was calculated from the date of surgery to sign(s) of progression (according to Macdonald's criteria) or death respectively. The data was analyzed using SPSS software (version 11.5). Cumulative survival and tumor control rates were calculated using Kaplan-Meier actuarial method. Univariate analysis was performed on the potential prognostic factors like extent of surgical resection, age of the patient, grade of tumor and KPS. The statistical significance levels were calculated using the log-rank test.

Results

Median follow-up of the study was 12 months with range of 1-57 months. Twenty seven patients (58.6%) had near total resection (NTR), 17 had sub total resection (STR) and 2 patients had biopsy only [Table 1]. Median dose of radiation delivered to PTV2 was 61.58Gy/30fr (range 48-62.4Gy) and to PTV1 was 54.3Gy (range 41-56.2Gy). 44 of 46 patients received concurrent TMZ and 35 of 46 patients received adjuvant TMZ (median 5 courses). Two patients received only adjuvant TMZ [Table 1].

For the whole group, median overall survival was 15 months and actuarial two-year survival was 39.4% ±7.7. Median progression free survival of the group was 9 months and two-year actuarial progression free survival was 33.2% ±7.1 [Figure 1]a, b. There was statistically significant superior actuarial two-year survival for patients with grade III tumor as compared to grade IV tumors (75% vs 24.3%; P = 0.003) [Figure 2]. Similarly, patients with KPS 70-100% had much better survival than patients with KPS of less than 70 (two-year survival of 66.5% vs 0%; P = 0.000) [Figure 3]. However, there was no significant impact of age on the outcome in our patient cohort (HR=1.46; 95% CI: 0.68-3.16). Although there was a

trend toward better overall survival for patients who had near total resection (NTR) of the tumor as compared to the ones who had subtotal resection (STR), but it did not reach statistical significance (HR= 1.41; 95% CI: 0.66-3.02). {Figure 1} {Figure 2} {Figure 3}

Dose to the normal brain (excluding PTV1) was assessed. Mean dose to 33% of the volume of the normal brain (D33) was 44.7Gy, to 50% of the volume (D50) was 36.8Gy and to 67% of the volume (D67) was 26.7Gy. Dose received by PTV1, PTV2 and critical structures like brain stem, optic nerve / chiasma, eyes, cochlea and normal brain parenchyma is depicted in [Table 1] and [Table 3]. {Table 3}

Thirty two of forty six patients had residual disease / recurrence at the time of last follow-up. Majority (90.6%) had residual or recurrent tumor within the clinical target volume (CTV). One patient had recurrence outside the CTV and 2 patients had multicentric recurrence. Twenty nine patients had since died and 17 patients were alive.

Magnetic resonance imaging neurotoxicity grades:

At three months following completion of radiation and TMZ, grade 1, 2 and 3 neurotoxicity was seen in 16.2 5.4 and 2.7% of patients respectively according to severity of white matter changes reported on various sequences of MRI [Figure 4]. Over a period of time, white matter changes in the MRI tended to be progressive in nature [Figure 5]. At two years following radiation and temozolamide, grade 1 and 2 neurotoxicity was seen in 35.3 and 29.4% patients respectively [Figure 4]. Only 1 patient developed grade 3 toxicity at 3 months. He survived till 15 months and then had recurrence and died. {Figure 4} {Figure 5}

Cognitive functions

Cognitive function at base line onwards is shown in [Figure 6]. At 24 months, 57.1% of patients had no neurocognitive deficit while grade I cognitive disturbance was noted in 42.8% of patients [Figure 6]. 2 patients (6.8 %) had grade II and 1 patient (3.4%) had grade III cognitive disturbance at 6 months. Two of these patients survived for 12 and 14 months respectively and 1 died at 7 months. {Figure 6}

Discussion

Delayed radiation injury in patients with high grade glioma has not been reported widely because of their limited life span and very high rate of local tumor progression. The risk of radiation induced brain necrosis is 5% at 60Gy. [9] Radiation necrosis causes significant morbidity from persisting cerebral edema and neurologic deficits. Late radiation toxicity also includes deterioration of cognitive and visual function. [9],[10] Available data for long-term survivors of high grade glioma indicates that dementia is common debilitation and cognitive decline has also been documented in patients receiving radiation for low-grade glioma. [10],[11]

Higher incidence of radiation necrosis has been reported in the context of accelerated fractionated radiation therapy and concomitant carboplatin based chemotherapy. [4] That series had reported radiation necrosis in 36 of 148 patients (24.3%) and additional 61 patients (41.2%) had MRI evidence of various radiation induced changes in the white matter or the cortex. Another series has reported brain necrosis in 3 of 18 patients (16.6%) with hypo fractionated IMRT for primary GBM. A dose of 50Gy was delivered within two weeks to enhancing primary tumor and 30Gy to the surrounding edema. Rest of the patients had grade 0-2 morbidity on radiation therapy oncology group neurotoxicity scores. [12]

Another factor which can enhance the radiation induced neurotoxicity is the frequent use of chemotherapy either sequentially or concurrently with radiation therapy. [2],[4] Recent advances in chemotherapy, especially with addition of TMZ to radiation therapy, have resulted in improved survival for patients with GBM. [1] Recently available data from phase III trial by EORTC Brain Tumor group,

Radiation Oncology group and NCIC clinical Trial group shows 2, 3 and 4 year survival figures of 27.3, 16.7 and 12.9% in patients of GBM treated with RT / TMZ arm. [13] Additional drugs like lomustine have been tried with radiotherapy and TMZ in an attempt to further enhance the survival in these patients. [14] Thus, a modest but significant proportion of patients would be long-term survivors who would be at higher risk of late radiation toxicity including radiation necrosis and neuro-cognitive deficits. [11]

Diffuse white matter abnormalities involving one or both cerebral hemisphere are discernible within few months following radiation therapy. MRI reveals more extensive area of white matter alterations including edema as compared to CT scans. [15],[16] Differentiation from tumor recurrence or progression may be difficult and often CT-PET and GHA SPECT are done to differentiate between the two. [15] 16 patients in our series had CT-PET or GHA/ Thallium SPECT to differentiate tumor recurrence from radiation sequelae / necrosis.

Cognition vs white matter changes

The association of pronounced white matter injury and intellectual impairment suggests a common underlying etiology for functional changes in adults and learning deficits in children. [17],[18] Symptoms related to white matter injury range from mild lassitude or personality change to marked incapacitating dementia. Progressive memory loss and dementia can be seen in cases with pronounced ipsilateral or diffuse bilateral changes in the MRI. [15],[19] Constine et al have reported white matter changes in MRI in their series of 41 patients treated with radiation (n =36) and radiation and bis-chloroethylnitrosourea (BCNU) (n=5) [Table 4]. [15] Also high dose region of radiation closely corresponded to the areas of intense white matter changes in the MRI. Major cognitive disturbance was associated with grade 3-4 changes on MRI in 71% of their patients as compared to grade 3-4 changes in 29% of the remaining adult group. [15]{Table 4}

In another series, around 50% of patients showed significant alterations in white matter signal following radiation therapy for intracranial tumors. [20]

Contributing factors such as higher radiation doses (>60Gy), fraction size above 2Gy, large radiation volumes and use of chemotherapy have been shown to increase the risk of late radiation effects. [21],[22],[23] Another factor which can enhance radiation toxicity is the uncertainty in target volume definition which may not only result in marginal misses of tumor but also in unnecessarily overdosing normal brain. [5] It is evident that non conformal techniques of radiation therapy give high dose to the normal brain and critical structures like optic nerve, chiasma, brain stem, cochlea etc which in turn can contribute to more pronounced MRI neurotoxicity grades.

IMRT plan yields superior target coverage as compared with 3D-CRT plan and it also enables substantial decrease in the volume of normal brain receiving high dose of radiation. [5],[7] It would have a bearing on late radiation toxicity ranging from neuro-cognitive decline on one hand to radiation necrosis at the other extreme. In the present series, mean volume of PTV1 was 454.26CC and the mean volume of normal brain (excluding PTV1) was 912.78CC. Thus, high-grade gliomas occupied approximately one third of the volume of normal brain and therefore, a large volume of normal brain parenchyma was at risk of getting exposed to high dose of radiation. Three-dimensional target volume delineation with the help of CT and CT-MRI fusion and radiation dose optimization with inverse planning resulted in substantial reduction in the volume of normal brain exposed to high dose of radiation. Mean dose of radiation delivered to 33, 50 and 67% volume of the normal brain in the present study was 44.7Gy, 36.8Gy and 26.7Gy respectively for a prescribed dose of 60Gy to PTV2 and 54Gy to PTV1.

Majority (70.6%) of the patients treated with this protocol of radiation and temozolamide had grade 0 or grade1 white matter changes in the MRI while 29.4% of patients had grade 2 MRI neurotoxicity at two years which is a reasonable period to assess this complication [Figure 4]. Only 1 patient had grade 3 white matter change persisting up to one year after treatment.

In the present study although there was some progression in white matter changes in the MRI, cognition did not worsen overtime [Figure 5]. Fifty seven percent of patients had no cognitive disturbance and 42.8% had only grade I cognitive disturbance at two years [Figure 6]. However, 3 patients had grade II cognitive disturbance at the time of commencement of radiation therapy which was attributed to the size and location of the tumor and the impact of surgery.

Severity of the white matter changes in the MRI (neurotoxicity grades) in the present study is much lower than that of other reported series [Table 4]. It can be explained by the reduction in the volume of normal brain receiving high dose of radiation due to three-dimensional target delineation and inverse planning associated with conformal radiation especially the IMRT. [24] In earlier studies, non conformal radiation techniques and large radiation portals were employed which would have contributed to the higher grades of white matter changes in those studies. Further, low grades of matter changes in the present series were associated with low grades of cognitive decline [Figure 4] and [Figure 6].

One of the concerns with highly conformal treatment delivery is the risk of missing the tumor due to sharp dose gradient outside the target volume. But despite the close margins used in these techniques, they do not increase the risk of marginal or distant recurrences. [25] In the present study also, there was no increase in marginal recurrences or geographical misses since 90.6% of the recurrences occurred within the PTV1. Only 1 patient [3.1%] recurred outside the PTV1 and 2 patients (6.2%) had multicentric recurrence.

Conclusion

Three-dimensional target delineation and conformal radiation therapy are associated with low grades of neurotoxicity and cognitive decline in patients with high-grade gliomas. This can have far reaching consequences on the quality of life of these patients who also receive concurrent chemotherapy in the form of temozolamide. Due to low incidence of treatment-induced neurotoxicity, further intensification of treatment with newer drugs seems feasible. However, more studies and longer follow up are warranted to further confirm these observations.

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