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Fractionated Stereotactic Radiotherapy in Pediatric Diffuse Intrinsic Brain Stem Gliomas

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Objective : We treated 10 pediatric diffuse intrinsic brain stem glioma(BSG) patients with Novalis system (linac based radiotherapy unit, Germany) and examined the efficacy of the Fractionated Stereotactic Radiotherapy(FSRT).

Methods : A retrospective review was conducted on 10 pediatric diffuse intrinsic BSG patients who were treated with FSRT between May, 2001 and August, 2004. The mean age of the patient group was 7.7 years old. Male to female ratio was 4 to 1. The mean dose of FSRT was 38.7Gy, mean fractionated dose was 2.6Gy, mean fractionation size was 16.6, and target volume was 42.78cm^3. The mean follow up period was 14 months.

Results : Four weeks after completion of FSRT, improvements on neurological status and Karnofsky performance scale(KPS) score were recorded in 9/10 (90%) patients and magnetic resonance imaging(MRI) showed decrease in target tumor volume in 8 pediatric patients. The median survival period was 13.5 months after FSRT and treatment toxicity was mild.

Conclusion : It is difficult for surgeons to choose surgical treatment for diffuse intrinsic BSG due to its dangerous anatomical structures. FSRT made it possible to control the tumor volume to improve neurological symptoms with minimal complications. We expect that FSRT is a feasible treatment modality for pediatric diffuse intrinsic BSG with tolerable toxicities.

KEY WORDS : Brain stem · Glioma · Radiotherapy.

Introduction

Brain stem glioma(BSG) accounts for 10~15% of all central nervous system tumors in children and 20~25% of all infratentorial tumors[19,21]. The majority of BSGs are biologically malignant intrinsic tumors that infiltrate extensively into the surrounding brain stem. Tumors arise predominantly in the pons. The prognosis of children with BSG is dismal : most patients die within 1 years of diagnosis, and median survival is less in children than adults[6,13,22]. Tumors arising in the brain stem can be grouped as focal, dorsal exophytic, cervicomedullary, and diffuse intrinsic tumor[3,8,15,23]. In pediatric age group, diffuse intrinsic BSG accounts for approximately 80% of all tumor arising in the BSG. Diffuse intrinsic BSG is present with greater tumor volume, cranial nerve deficits at diagnosis, and short duration of these symptoms; and it remains inaccessible to surgical resection. The addition of chemotherapy does not seemed to improve outcome of patients with diffuse disease and short symptom histories either[2]. The amount of administered radiotherapy is limited to tolerance of brain stem. Over the last 10 to 20 years, the Pediatric Oncology Group has undertaken sequential clinical trial in an attempt to develop more effective treatment[7,12]. Standard treatment for diffuse intrinsic BSG consists of conventional radiotherapy using local field and dose of the order of 54Gy over 6 weeks using once daily fraction[5,13,14,22]. Recently, new treatment modality such as Fractionated Stereotactic Radiotherapy(FSRT) and Gamma Knife Radiosurgery are used instead of conventional radiotherapy[6,17,21]. We evaluated the effectiveness of FSRT in management of patients with surgically unresectable pediatric diffuse intrinsic BSG.

Materials and Methods

Ten patients with diffuse intrinsic BSG were treated between May, 2001 and August, 2004. Patients who were isolated as young age group (from 3 to 15 years old) were eligible for the trial if they had a clinical and radiographic diagnosis of a BSG. Male to female ratio was 4 : 1 with the mean age of

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7.7 years. In this group, three patients underwent stereotactic biopsy and three were diagnosed with high-grade gliomas. Seven patients present with typical tumor appearance on MRI were treated without histological diagnosis confirmation because the risk of biopsy appeared higher than treating without precise diagnosis[1]. On MRI, most tumors appeared hypointense on T1-weighted image and hyperintense on T2-weighted image at diagnosis. Gadolium enhancement on T1-weighted MRI was present in 7 patients. The presenting symptoms and signs of each patient are shown in Table 1. A patient may have had more than one symptoms and signs at the time of presentation. The most frequent symptom during diagnosis is cranial nerve deficits and the second is ataxia. Cranial nerve deficits are shown in Table 2. The median KPS score at the time of presentation was 60 (range from 50 to 80). Three patients have been treated for recurrent tumors. Two of these three patient were reirradiated and the other patient received combined FSRT and chemotherapy treatment. We irradiated these patients using Novalis system at about 38.7Gy on average (range 21~54Gy), applied to the 80% isodose line and fractionated dose at 2.6Gy per day on average (ranging from 1.8 to 3.5Gy per day). Average fractionation size was 16.6 (ranging from 6 to 30). The usual radiotherapy dose was 45Gy given in 15 fractions of 3Gy. For recurrent BSGs after RT, we irradiated a reduced total dose. Mean target volume was 42.78cm^3, ranging from 9 to 76cm^3, before FSRT(Table 3). Mean follow-up period is 14 months (from 6 to 41 months). To assess clinical and radiological tumor response, all patients received follow-up MRI, KPS score and neurological examination 4 weeks after completion of Novalis and 3 months thereafter. If T2-weighted MRI showed reduction in size for high signal intensity regions, radiological response was assumed. The prognosis was classified as the follows : complete response(CR) if tumor and edema completely disappeared, partial response(PR) if size of the tumor shrunk by more than 50%, stable disease(SD) if size of the tumor shrunk by less than 50% and neurological examination and KPS score are stable; and progressive disease(PD) if the tumor increased in size or neurological examination worsened even if the tumor size remained the same.

Table 1. Symptoms/signs at presentation (n=10)

Symptoms/signs	Number	%
Cranial nerve deficits	10	100
Ataxia	7	70
Nausea/vomiting	1	10
Hydrocephalus	3	30
Paresthesia	1	10
Headache	2	20
Nystagmus	2	20

Table 2. Cranial nerve deficits as a initial presentation

Cranial nerve	No. of cases
III, IV	3
V	0
VI	5
VII	1
VIII	0
IX, X, XI	4
XII	0

Results

Tumor size decreased in 8(80%) patients(Fig. 1), 2(20%) had stable disease and none had tumor progression during the first MR imaging evaluation (4 weeks after the treatment). The response or stabilization rate for the 10 evaluable patients was 100%. At follow-up MRI (12 weeks later), the response or stabilization rate was 80% as follows : one complete response, six partial responses, one stable disease, and two progressive diseases. Reduction of the target volume was 20.2cm^3 on average (ranging from 4.5 to 55cm^3). One patient displayed nearly complete reduction of target volume and so far reported no recurrence or distant metastasis for over 41 months(Fig. 2). Prior to FSRT, three out of 10 patients presented with a KPS score$\geq$70. All of these patients showed an increase of KPS score within 4 weeks after FSRT. The KPS score was improved by 20 points after FSRT and remained stable for 12 weeks. The other seven out of 10 patients presented with KPS score of <70 prior to FSRT. Six of these patients showed an increase in KPS score within 4 week, but one patient remained unchanged. In total, Nine

Table 3. Summary of the cases (n=10)

Case	Sex/ Age	Volume (cm^3)	Dose (Gy)	Fx dose(Gy)	Fx size	Operation before FSRT	Treatment before FSRT	Survival time (month)	R.R.	KPS Pre	KPS Post	KPS 3m
1	M/8	14.06	21	3.5	6	Biopsy	RT, 54Gy	10	SD	50	60	60
2	F/9	76.23	30	2	15	Shunt	RT, 25Gy	14	SD	50	50	50
3	M/8	35.10	54	1.8	30	Shunt	-	6	PR	50	50	50
4	F/8	9.12	51	3	17	Shunt & Biopsy	-	14	PR	60	80	80
5	M/6	66.00	45	3	15	-	-	*9	SD	80	80	80
6	M/5	10.10	45	3	15	-	-	*41	CR	60	100	100
7	M/9	9.70	39	3	13	Biopsy	-	13	PR	50	70	70
8	M/11	39.03	45	3	15	-	-	20	PR	60	70	80
9	M/3	64.75	50	2	25	Shunt	-	19	SD	60	80	80
10	M/4	37.23	30	2	15	Shunt	FSRT, 30Gy	9	SD	50	50	40

Abbreviation : * = alive, RT = Radiotherapy, FSRT = Fractionated stereotactic radiotherapy, Fx = Fractionation, R.R = radiologic resopnse, pre = previous FSRT, post = post FSRT, 3m. = 3 month after FSRT

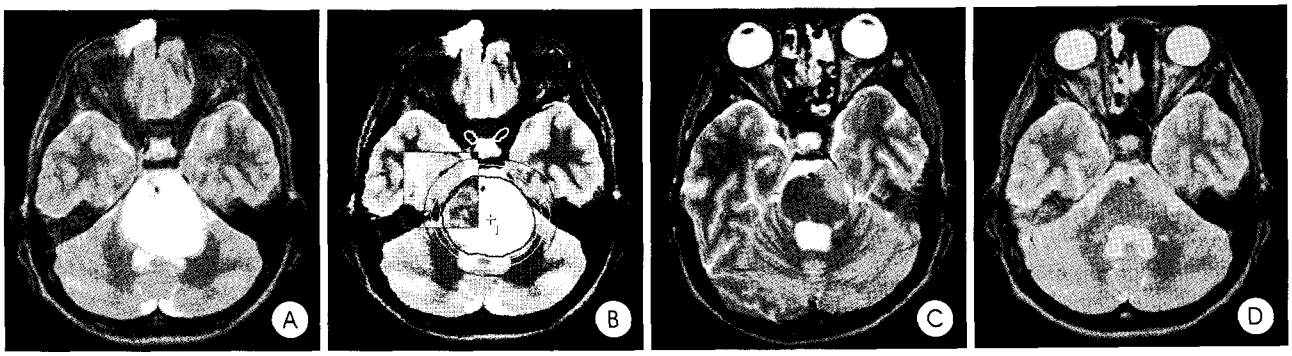

Fig. 1. A : Pre-fractionated stereotactic radiotherapy brain T2-weighted magnetic resonance(MR) image shows the growth pattern of diffuse intrinsic type. B : Dosimetry of fused image of T2-weighted and T1-wighted gadolinuim enhancement MR images. Radiotherapy dose was 52.5Gy given in 30 fractions of 1.8Gy isodose at 80% (applied prescribed dose line is painted yellow). C : One month after fractionated stereotactic radiotherapy, T2-weighted MR image demonstrates marked decrease size of the tumor. D : Three months after fractionated stereotactic radiotherapy, MR image shows stable residual mass.

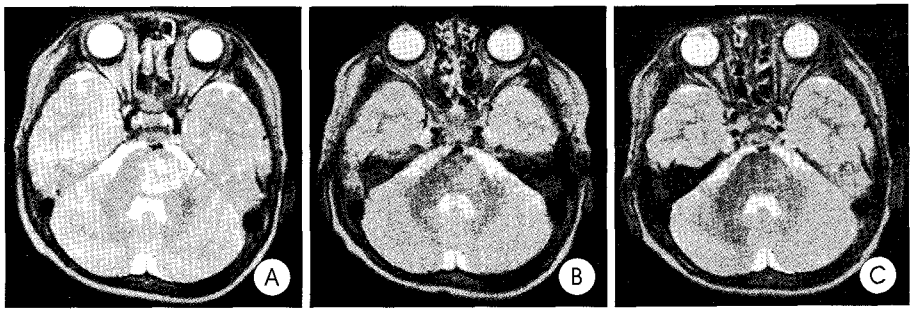

Fig. 2. A : Brain T2-weighted magnetic resonance(MR) imaging demonstrates diffuse intrinsic tumor. B : One months after fractionated stereotactic radiotherapy, the follow-up MR image reveals decrease in size of the tumor. C : Three months after FSRT, MRI shows complete response of the tumor.

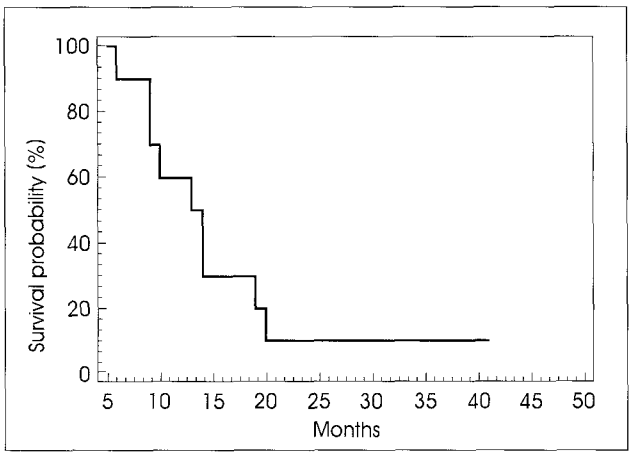

Fig. 3. Kaplan-Meier survival curve estimates of the probability of overall survival after fractionated stereotactic radiotherapy, n=10.

of 10 patients showed increased a KPS score within 4 weeks after FSRT and remained stable for 12 weeks. Two of 10 maintained the KPS over 12 months and then aggravated but one is still alive over 41 months without any neurologic aggravation.

Neurological symptoms improved in 9 patients 4 weeks after FSRT completion. Five patients developed hydrocephalus during the follow-up period and received ventriculo-peritoneal shunt treatment. However, it is the complication of BSG itself, not as a result of FSRT. Treatment related acute toxicity included vomiting in one patient and headache in one. No other toxicity was reported. The estimated median survival of these patients was 13.5 months after FSRT(Fig. 3).

Discussion

Approximately 80% of brain stem gliomas in the pediatric age group are diffuse intrinsic lesions. Diffuse intrinsic BSGs generally present with an insidious onset of symptoms that most commonly result from involvement of corticospinal tract, cranial nerves, and cerebellum. The diagnosis is generally made based on a typical aspect on the MRI, precluding the need for histological confirmation. A typical brain MRI shows an intrinsic, pontine base infiltrative lesion that exerts significant mass effects on adjacent structures. Feature that correlate with particularly adverse outcome include short duration of clinical history, presence of cranial nerve deficits at diagnosis, pontine location, greater volume of tumor, degree of brain stem enlargement, MR image findings such as a poorly circumscribed tumor, and presence of peritumoral hypointensity, and ring enhancement that suggests high-grade histology[11,15,16,20,23]. Unfortunately, children with these tumors usually have a short history at presentation and display multiple neurological deficits, and their outcomes are uniformly poor[12,18]. Surgery has no role in the management of patients with diffuse BSGs because high morbidity and mortality rate associated with any degree of resection of intrinsic BSGs[1]. The addition of chemotherapy did not appear to improve the outcome of patients with diffuse disease and short symptom histories[2]. Current treatment for diffuse intrinsic BSG consists of conventional radiotherapy using local fields and doses of the order of 54Gy over 6 weeks using once daily fractionation, which produces temporary

neurological improvement in at least 70~80% of patients[10]. Nevertheless, the median time to tumor progression is of the order of only 6 months and the median survival time after treatment is less than 1 year. Due to the poor prognosis of children with BSG, especially high-risk patients, several trial that utilize hyperfractionated radiotherapy(HFRT) initiated. HFRT, which delivers a large number of small fractions of radiation, could be a promising method to control tumor growth without increasing neurological toxicity[10,13,22]. Freeman[10] reported the median time to disease progression was 6 months and the median survival time was 10 months for children with diffuse intrinsic BSGs who were treated with hyperfractionation (70.2Gy given in 60 fractions of 1.17Gy). The low frequency of neurological toxicity in this method is attributed to the differences in repair capacity between normal brain and tumor cell. Freeman et al.[11] report the results of a Pediatric Oncology Group study using concurrent cis-plantinum and HFRT. This study suggested that the patients treated with the combined chemoradiotherapy approach had worse outcome than those treated with radiotherapy alone. Packer et al.[3] claim that higher doses of RT may cause up to 15% intralesional cystic/necrotic changes within 8 weeks of completion of treatment with impairment of neurology after HFRT at 72Gy as a sequele of therapy. But, some authors[21] report HFRT treatment related toxicity rates as 40% in the form of skin reaction, otitis media and externa, ear pain, tinnitus and hearing loss. Therefore, advantage of precise dose delivery and sparing of tissue probably become more important as most of new pediatric treatment protocols for BSGs follow this trend. In comparison to conventional conformal RT, FSRT allows precise target point positioning and dose delivery especially in tumors close to inner ears without disproportional expenditure. Schulz-Ertner et al.[21] treat 41 patients with BSGs using FSRT. A mean total dose of 54Gy was given in daily fraction of 1.8Gy. Six weeks after FSRT, the result showed that 19/41(46.3%) displayed improvement in neurological symptoms, ten(24.4%) remained stable and one patient had ototoxicity. Based on these results, Schulz-Ertner et al.[21] claim FSRT is a feasible treatment modality for BSGs because of its tolerable toxicity. As developing brain, brain stem, and peritumoral edematous brain are vulnerable to radiation injury. Children with BSGs who received high doses of radiation experience clinical deterioration. It has been reported that certain chemotherapeutic agents such as carmustine, procarbazine, dibromodulcitol, methotrexate, actinomycin D, and vincristine may accelerate or aggravate radiation injury. In 1951, Leksell[24] combined the techniques of stereotaxy and radiation treatment and coined the term "stereotactic radiosurgery". Linear accelerator radiosurgery (LINAC) was first described in 1984 by Betti and Derechinsky[4,17]. The evolution and adaptation of LINAC to stereotactic radiosurgery provided a more popular treatment modality. The Novalis equipment used in this research was designed exclusively for stereotactic radiosurgery. A micromultileaf collimator is permanently mounted on the LINAC, and various sizes of circular collimators can be used[24]. Fractionated radiotherapy increases the cellular reoxygenation and redistribution of the target volume and allows repairing of sublethal or potentially lethal radiation damage in surrounding normal tissues. FSRT combines the precision of stereotactic positioning with the radiobiological advantage of fractionation. In malignant glial tumors, radiotherapy has been used for boost irrdiation, in addition to conventional fractionated radiotherapy.

We treated pediatric diffuse intrinsic type of BSGs with FSRT using Novalis. In all cases, field shaping was perfomed with a micromultileaf collimator to optimize dose distribution in nonspherical tumors. the collimator consist of 26 pairs of leaves varying in thickness from 3 to 5.5mm. Treatment was administered through six noncoplanar dynamic arc. The planning target volume was encompassed by an 80% isodose line. Median time to progression was 7 months, and median survival time was 13.5 months after FSRT. Comparing to the former treatment, which included conventional RT, HFRT, FSRT, we used relatively low radiation doses for a short period of time. Noticeably, FSRT using Novalis in the treatment of pediatric diffuse intrinsic BSGs showed that KPS and neurological symptoms improved immediately without acute side effects. In most treated patients, we oberved mass size reduction on follow-up MRI.

Conclusion

FSRT is a feasible treatment modality for pediatric diffuse intrinsic BSG with minimal toxicity. FSRT that uses Novalis shaped beam device presents effective and safe non-invasive treatment modalities for pediatric diffuse intrinsic BSG. FSRT made it possible to control the tumor volume to improve neurological symptoms and KPS with minimal complications. Due to insufficient number of patients and inadequate follow-up period for our group of FSRT patients, this modality requires further investigation regarding optimal dose/fractionation scheme to determine the most efficient treatment mode. In addition, radiobiological study is necessary.

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Commentary

The authors found that FSRT that uses Novalis shaped beam device presents effective and safe non-invasive treatment modalities for pediatric diffuse intrinsic BSG.

The shorter duration of symptoms prior to diagnosis in the diffuse pontine tumour group can be explained by the fact that diffuse tumours are typically malignant fibrillary astrocytomas (grade III or IV). Magnetic resonance imaging scans have revolutionized the understanding of brainstem tumours and have improved the diagnosis of this neoplasm, avoiding in many cases the use of invasive procedures such as biopsies. Most brainstem gliomas have a homogeneous and hypointense image on T1-weighted images and iso- or hyperintense on T2-weighted images. The pattern of enhancement is variable and can be diffuse, nodular or ring-shaped around the margins of a cyst, or a necrotic area. Although numerous groups have studied the prognostic value of contrast-enhanced MRI in brainstem gliomas, the results of those studies have been inconclusive.

Radiotherapy had been the recommended treatment for all brainstem gliomas, but now is used more selectively. For a patient with a diffusely infiltrative brainstem glioma, standard treatment remains conventional external beam, local field radiotherapy to a dose of 54 to 60Gy in 6 weeks. Without radiation, median survival is approximately 20 weeks. Radiotherapy results in a worthwhile, albeit temporary, improvement in neurologic function, though the overall prognosis for such a patient remains dismal. Increasing the radiation dosage beyond 60Gy has not proved effective. With hyperfractionation, using total doses of 64Gy or higher, delivered in twice daily, smaller dose fractions over 6 weeks, failed to yield additional survival benefit.

A series of radiation dose escalation studies used hyperfractionated radiotherapy(HRT) with doses from 64.8Gy to 78Gy, in a twice daily schedule with an interfractional interval of no less than 6 hours. At the highest radiation dose levels, corticosteroid dependency, vascular events, white matter changes, hearing loss, hormone deficiencies, and seizures were observed. There was no improvement in event-free survival or survival using HRT, thus leaving conventional radiotherapy as the radiotherapeutic regimen of choice for children with newly-diagnosed brain stem glioma. It is not clear that what is optimal number of stages and dose per stage and what is the optimal time interval between stages in FSRT. This article fell short of my expectations on that point. Further investigation requires optimal dose/fraction scheme to determine the most efficient treatment.

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