Multiple Daily Fractionated RT for Malignant Glioma

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Since Jan. 1992, authors have conducted a pilot study to treat malignant glioma with multiple daily fractionated(MDF) radiation therapy and this paper presents the outcome compared MDF to conventional factionated(CF) radiation therapy. Between Sep. 1989 and Jan. 1993, forty three patients with high grade glioma of brain except brain stem glioma were treated: nineteen patients were treated with CF radiation therapy and 24 patients were treated with MDF radiation therapy. In CF radiation therapy, total dose was 6300cGy/35fx in 7 weeks, which 5040cGy was delivered to the initial target volume and 1260cGy to reduced target volume. And in MDF radiation therapy, total dose was 6400cGy/40fx in 4 weeks, which 3200cGy was delivered to the initial target volume as 160cGy 2 times daily 6hr apart. All patients had histologically confirmed anaplastic astrocytoma(AA) of glioblastoma multiforme (GBM) with stereotactic biopsy or craniotomy for subtotal or gross tumor resection. The range of follow-up was 7 months to 4 years with a median follow-up of 9 months.

The Median survival from surgery was 9 months for all patients. The median survival was 9 months and 10 months for MDF group and CF group and 10 months and 9. 5 months for glioblastoma multiforme and anaplastic astrocytoma, respectively. In 36 patients with follow-up CT scan or MRI scan, disease status was evaluated according to treatment groups. Four patients(GBM:3, AA:1) of 21 patients in MDF group, were alive with no evidence of disease, while none of patient was alive with no evidence of disease in CF group. The progression of disease had occurred in 20 patients, 11 patients and 9 patients in MDF group and CF group, respectively. All of these patients showed in-field progression of disease. Four of 11 patients(27%) in MDF group showed the new leasion outside of the treatment field, while 5 of 9 patients(56%) in CF group. In our study the prognosis was not influenced by age, KPS, grade, extent of surgery and different fractional scheduled radiation therapy. Authors concluded that MDF regimen was well tolerated and shortened the treatment period from 7 weeks to 4 weeks without compromising results. We believe that further follow-up is needed to assess the role of MDF.

Key Words : Malignant glioma, multiple daily fractionation

INTRODUCTION

Malignant glioma comprise 33% to 45% of primary brain tumor and of these, nearly 85% are glioblastoma multiforme[1-3]. The overall survival for malignant glioma with postoperative radiation therapy is reported 9 to 12 months. The 5 year survival rate is 10-35% for patients with anaplastic astrocytoma and zero for patients with

glioblastoma multiforme histology[4-6]. With few exception, there has been little improvement in the outcome of patients with malignant gliomas over the past decade. The grim outlook for patients with malignant glioma is due to the failure of local control. The greatest improvement in survival has been achieved with the addition of postoperative irradiation[7]. However the response of these lesion to standard radiotherapeutic technique is limited by their striking inherent radioresistance and radiosensitivity of surrounding normal brain tissue[8]. The current research strategies have focused on methods designed to enhance the effectiveness of external irradiation using hypoxic cell radiosensitizers, halogenated pyrimidine analogs, chemotherapy and altered fractionation schemes, or to selectively augment the tumor dose using interstitial brachytherapy.

The tolerance of the brain depends on the size of the dose per fraction and the total dose administered. The tolerance of normal brain has generally been accepted as about 60Gy delivered by conventional fractiontion with 1.8-2.0Gy given daily. Sheline et al proposed the formula for isoeffective dose of neural tissue (termed neuret): Neuret=Total dose x $N^{-0.41}$ x $T^{-0.03}$, where N is the number of fractions and T is the total time in days. They suggested that the threshold dose for brain injury are approximately 1260-1270 neuret (Table 1)[9].

The use of hyperfractionation provides the possibility of increasing local control without increasing toxicity due to late effects. Additional potential theoretic benefits of hyperfractionation include increased tumor cell kill because of (a) the amount of accumulation and repair of sublethal radiation injury is decreased by the use of small doses, and (b) the redistribution of actively proliferating cells through the cell cycle allows for progression of some cells into more radiosensitive phases by the time the second daily dose is given[10]. For hyperfractionation delivered in doses of 1.1 or 1.2Gy per fraction twice daily seperated by 4-8 hr, the initial radiobiologic estimations were that the total RT dose could safely be increased by 10%. The Brain Tumor Cooperative Group(BTCG) evaluated 1.1 Gy twice daily to 66Gy and found no difference in survival when compared with conventional fractionation. In the RTOG phase II fractionation trial 8302 patients received dose of 48 and 54.4Gy at 1.6Gy/fx twice daily with BCNU. The median survival time was compared favorably with the similar patients treated conventionally in RTOG trial 7918. The RTOG 85-23 was a phase I/II dose escalating trial in patients with brain metastasis, the patients received 1.6Gy twice daily seperated by 4-8 hour delivered 5 days a week. The entire brain was treated to 32Gy and boost dose escalated from 16 Gy to 22.4Gy, 32Gy and 42.4Gy (total 48Gy to 74.4Gy). They observed no undue toxicity with escalating dose of irradiation[12].

In this study, the choice of the 64Gy (1279 neuret) with 1.6Gy/fx, 2 times daily 6 hours apart was based upon the clinical and biological data. This regimen was compared to conventional fractionation regimen of 63Gy with 1.8 Gy per fraction.

Table 1. Threshold Dose of Brain Injuries

Total dose(Gy)	No.of Fraction (elapsed days)	[1]Neuret
35	10(14)	1264
60	35(49)	1244
76	60(42)	1268
[2]64	40(28)	1279

1) Neuret(isoeffective dose) in brain by Sheline GE.
Neuret=Total Dose x $N^{-0.41}$ x $N^{-0.41}$ x $T^{-0.03}$
N:No. of fraction
T:Total treatment time in days (elapsed days)
2) This regimen was used in this study.

METHODS AND MATERIALS

1. Patient population

Forty three patients with high grade glioma of brain except brain stem glioma were treated between January 1989 and January 1993. All patients had histologically confirmed anaplastic

astrocytoma (AA) or glioblastom multiforme (GBM) with stereotactic biopsy or craniotomy for subtotal or gross tumor resection. Histologic classification is based on the criteria of Daumas-Duport grading system. Patients were classified according to the known prognostic indications of age, performance status, surgical methods and histology. Stereotactic tumor biopsy was carried out in 13(MDF:8, CF:5) patients and cranitomy for subtotal or gross tumor resection in 30(MDF: 16, CF:14)patients. Anaplastic astrocytoma was found in 15(MDF:6, CF:9) patients and glioblastoma multiforme in 26(MDF:16 CF:10) patients. Karnofsky performance status(KPS) was less than 70 in 8(MDF:4, CF:4) patients and 70 or greater in 32(MDF:20, CF:12) patients. 25(MDF: 14, CF:11) patients were more than 50 years of age and 18(MDF:10, CF:8) were less than 50 years of age. The range of age of patients was 2 years to 78 years with a median age of 52.5 years.

Table 2. Patients Characteristics

	MDF(N=24)	CF(N=19)
Sex		
M/F	14/10	10/9
Age		
<50	10	8
>50	14	11
K.P.status		
<70	4	4*
>70	20	12*
Surgery		
Biopsy	8	5
Resection	16	14
Pathology		
GBM	18	10
AA	6	9

K.P.:Karnofsky performance
MDF :multiple daily fractionation
CF : conventional fractionation
GBM :glioblastoma multiforme
AA :anaplastic astrocytoma
* Three patients of 19 patients was not defiened initial performance status

The interval between surgery and the commencement of radiation therapy had to be no longer than 4 weeks. The patients were classifified by age, KPS, histologic types and surgical methods in each group. The characteristics of patients were summarized in Table 2. The pretreatment evaluation included medical history, physiccal examination, neurologic examination, evaluation of performance status, CBC, biochemical survey, preperative computerized tomography (CT) or magnetic resonance imaging (MRI) with contrast to determine the target volume and postoperative CT or MRI scan as a baseline for the purpose of evaluating tumor response or progression after radiation therapy.

Patients were followed for neurological function, toxicity, disease progression and survival. Patients were examined every I month after completion of treatment for 6 months, then every 3 months for 2 years and thereafter every 6 months. CT or MRI scan were done I month after the completion of radiation therapy, then every 3 months and at time of neurological deterioration. Patients were considered to have treatment-related neurologic deterioration if this decline occurred eith: (a) in the absence of radiologic evidence of tumor: (b) with radiologic evidence of tumor responding to treatment: or (c) in the presence of compelling clinical or pathological evidence that a radiologic abnormality was treatment and not tumor related. Tumor progression was defined as increased enhancing tumor volume on CT scan or MRI scan and/or neurological deterioration for which no explanation other than tumor progression could be found.

2. Radiation therapy

Between Sep. 1989 and Dec. 1991. nineteen patients received conventional fractionated radiation therapy (CF RT, 6300cGy, 35 fractions, 7

weeks). Between Jan. 1992 and Jan. 1993 twenty four patients received multiple daily fractionated radiation therapy (MDF RT, 6400cGy, 40 fractions, 4 weeks, given as 160cGy 2 times daily 6 hours apart). Radiation therapy was administrated with 4-15 MV photon after completely healing of surgical wound. Initial target volume was defined as 2cm margin from the edema surrounding contrast enhancing lesion on the preoperative CT or MRI scan. Reduced target volume was defined as 2cm margin from the enhancing lesion on the preoperative CT or MRI scan. In conventional fractionated radiation therapy, the total dose was 6300cGy, which 5040cGy was delivered to the initial target volume and 1260cGy to reduced target volume in 7 weeks. In multiple daily fractionated radiation therapy, the total dose was 6400cGy which 3200cGy was delivered to the initial target volume and 3200cGy to reduced target volume as 160cGy 2 times daily 6 hours apart.

3. Statistical Methods

Survival was measured from surgery or biopsy to time of death regardless of cause, or the time of the last follow-up if patient was alive. Survival rate were calculated according to Kaplan-Meier method. Statistical analysis of survival of the different group of patients was carried out using logrank and Wilcoxon tests. A difference with a p value of less than 0.05 was considered as significant. The parametric multivariate analysiss was used to test whether the following covariates had a significant impact on survival: age (< 50 years vs≥ 50 years), KPS (< 70 vs ≥ 70), histology (AA vs GBM), extent of surgery (biopsy only vs resection) and types of treatment (MDF vs CF)

Table 3. Median Survival

	Median Survival (MO)	
Overall(43)	9	
Fractionation Schedule		
MDF(24)	9	
CF(9)	10	P>0.05
Histology		
GBM(28)	9.5	
MDF(18)	9.5	
CF(10)	10	P>0.05
A(15)	9	
MDF(6)	8.5	
CF(9)	9.5	P>0.05

MDF : multiple daily fractionation
CF : conventional fractionation
GBM : glioblastoma multiforme
AA : anaplastic astrocytoma

RESULTS

The range of follow-up was 7 months to 4 years with a median follow-up of 9 months. Median survival for MDF and CF group according to histologic type of GBM and AA was 9 months, 10 months and 9.5 months, 9 months respectively. There was no significant difference in median survival in patients treated with MDF radiation therapy compared to those treated with CF radiation therapy (Table 3). of the 43 patients, 36 patients were evaluated with follow-up CT scan or MRI scan and remainder were evaluated with neurologic examination. The range of follow-up of these 36 patients was I month to 11 months with a median 4 months. In 36 patients with follow-up CT scan or MRI scan, and remainder were evaluated with neurologic examination. The range of follow-up of these 36 patients was

Table 4. Disease Status of 36 patients with Evaluable CT or MRI

Status	MDF		CF		Total
	GBM(18)	AA(5)	GBM(6)	AA(7)	
Progression	10	1	5	4	20
Stable	5	3	1	3	12
NED	3	1	0	0	4

MDF : multiple daily fractionation
CF : conventional fractionation
GBM : glioblastoma multiforme
AA : anaplastic astrocytoma
NED : no evidence of disease

Table 5. Pattern of Progression

Progression(new lesion)	MDF	CF	Total
GBM	10(3)	5(2)	15(5)
AA	1(0)	4(3)	5(3)
Total	11(3)	9(5)	20(8)

GBM : glioblastoma multiforme
AA : anaplastic astrocytoma
New lesion : recurrence at outside of irradiated volume.

I month to 11 months with a median 4 months. disease status was evaluated according to treatment groups (Table 4). Of 21 patients in MDF group, 4 patients (GBM : 3, AA : 1) were alive with no evidence of disease, while none of patients was alive with no evidence of disease in CF group. The progression of disease had occurred in 20 patients, II patients in MDF group and 9 patients in CF group. Four of II patients(27%) in MDF group showed the new lesion outside of the treatment field, while 4 of 9 patients (56%) in CF group (Table 5). Age, KPS, histologic grade, extent of surgery and types of treatment had no significant influence on the prognosis. The MDF regimen was found to be well tolerated by patients and no major complications were noted during or after treatment. In all 24 patient, there was no alteratioin of radiation schedule because of toxicity.

DISCUSSION

Brain Tumor Cooperative Group(BTCG) trial 6901 provided evidence supporting the efficacy of radiation therapy in the treatment of malignant gliomas[13] and BTCG(6601, 6901, 7201) demonstrated a radiation dose response curve in a review of several studies.[14]. Survival increased from 50Gy to 55Gy to 60Gy. The RTOG(7401)-ECOG(1374) intergroup study, failed to demonstrate a significant increase in survival with increase in radiation therapy dose from 60 to 70Gy[10]. Based on these studies, the conventional fractionation schedule used in most clinical trials has been 60Gy given in single daily fractions of 1.72 to 2Gy, 5 times per week[15]. However, there has been little improvement in the outcome of patients with malignant glioma past decade. Most patients with malignant glioma have shown local tumor persistence and/or recurrence. Then, to improve local control, efforts over the years have focused on increasing the dose of radiation therapy delivered to the tumor. We need radiobiological understanding for tolerable dose of normal brain tissue and cytokinetics of glioma cell. The tolerance of normal glial and vascular tissues limits the amount of radiation that can be delivered to brain tumors[15]. Compared with neoplastic glioma cell, these tissues exhibit a slow rate of absence of cell division and have a greater capacity to repair sublethal radiation damage. Therefore, the tolerance of these tissues to radiation should be improved by reducing the size of the fractional dose[16]. Since tumor cell death is influenced more by total dose than by fraction size, there could be a therapeutic advantage to using a larger number of smaller fractions. Hyperfractionation is the use of two or more treatments per day, with fraction sizes smaller than conventional dose fractions, to deliver a higher dose in the same overall treatment time as conventionally fractionated therapy. With hyperfractionation, tumor control probabilities should improve without increasing the risk of late complications. Furthermore, with a 4 to 8 hour interval between doses there is greater probability that rapidly proliferating tumor cells will be irradiated during more radiosensitive phases of the cell cycle. Thus, proliferating tissue may "self sensitization" occurs during irradiation. MDF in this study showed no significant benefit for tumor control and survival. The total dose in MDF regimen was not incresed, and therfore the lack of a significant survival gain may be due to the fact that the total dose was too low to provide a detectable benefit over conventional fractionation. The RTOG has completed a hyperfractionation protocol for malignant glioma in which patients were randomized among total dose of 6460cGy, 7200cGy, 7680cGy and 8160cGy delivered in 120cGy fractions administered twice daily and separated by 4-6 hours[10]. The RTOG was resulted that the best survival occurred in patients treated with 72Gy (median survival of 12.8 months overall, and 14 months for the 72Gy) and 72Gy delivered by 120cGy twice daily is no more toxic than 60Gy delivered by conventional fractionation. The RTOG has activated a phase III study (RTOG 9006)

comparing MDF radiation therapy to 72Gy delivered in 1.2Gy fractions b.i.d. with 60Gy deivered by only daily fractions of 2Gy.

Anaplastic astrocytoma in this study showed somethat inferior survival compared to the published datas (Median survival 9 months in this study vs. about 20 months in best reported data). Although we can not explain more clearly, we think that in most patients with anaplastic astrocytoma only stereotactic biopsy was done and so this leads to misclassification considering with the heterogeneity of astrocytoma. The expression of histologic features may vary widely within astrocytoma[17,18]. Even within high grade region, there is various expression of critical diagnostic features[19]. Many high grade astorcytoma contain areas that are well differentiated. Biopsy in lower grade area in high grade glioma may be misclassified on diagnosis. Thus, the regional heterogeneity has profound implication on the diagnosis and grading of astrocytoma and may yield significantly different results.

The progression of diease had occurred in 20 patients in this study. Eight of 20 patients recurred in outside of treated area. This result suggest that high grade glioma may be infiltrated diffusely. and occurred with multicentric gliomas[17,20]. This growth pattern of high grade glioma has important implication in the planning of local therapy. Two point of wiews have been discussed for the planning of radiation therapy. One is that patients should receive limited field irradiation, with the hope of avoiding mental deterioration in the few long-term survivors. The oppsite argument is that patients should receive whole brain radiation therapy in order to treat all potential sites of tumor infiltration in all patients. While both points of view have merit, they must be reconciled with the fact that many patients will die of their disease within 1 year of diagnosis, regardless of the radiation field used. The bulk of retospective data available do not show a survival advantage to large versus small field irradiation[21]. Current recommendation for design of limited radiation field are based largely on pattern of failure studies by Hochberg and Pruitt and Wallner et al[22,23].

BTCG, RTOG and ECOG brain tumor studies have investigated pretreatment charateristics of patients that affact the outcome of patients with malignant glioma[24]. Histology, age and performance status are known to be the most important prognostic factors[25,26]. However, these variables have not been consistently observed or examined across all data sets. In this study, age, performance status and histology had no significant influence on the prognosis.

We concluded that the MDF radiation therapy used in the study yield survival results equvalent to CF radiation therapy. This study suggests that MDF regimen is well tolerated and is able to shorten the treatment period from 7 weeks to 4 weeks without compromizing results. We think that further follow-up is needed to assess the role of MDF. And we may consider MDF radiation therapy combining with gammar-knife therapy or interstitial brachytherapy as one approach to augmenting radiation dose.

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=국문초록=

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양광모 • 장혜숙 • 안승도 • 최은경

본 연구는 1989년 1월부터 악성성상세포종과 다형성 교아종에 대해 시행된 방사선 치료에 다분할 방사선 치료와 단순분할 방사선 치료와 단순분할 방사선 치료에 대한 효과를 비교하고 이들 뇌종양의 방사선치료후 예후에 영향을 미치는 인자를 확인하기 위해 시행되었다. 뇌간의 교종 환자를 제외한 전체 43명의 환자는 조직학적으로 악성성상세포종과 다형성교아종으로 확인되었고, 모두 방사선치료를 받았다. 환자는 일반적으로 알려진 예후인자인 연령, 성별, 수행능력, 조직학적 형태, 종양의 절제정도에 따라 분류하였다. 정위적 조직 생검만 시행한 경우는 13명으로 다분할 방사선 치료군과 단순분할 방사선 치료군에서 각각 8명, 5명이었고 개두술에 의해 종양절제술을 받은 경우는 30명으로 다분할 방사선 치료군과 단순분할 방사선 치료군에서 각각 16명과 15명이었다. 조직학적 소견에 따라 악성성상세포종은 15명으로 다분할 방사선 치료군과 단순분할 방사선 치료군에서 각각 6명, 9명이었고 다형성교아종은 26명으로 다분할 방사선 치료군과 단순분할 방사선 치료군에서 각각 16명, 10명이었다. 수행 능력이 70이하인 경우는 8명으로 다분할 방사선 치료군과 단순분할 방사선 치료군에서 각각 4명이었으며 대부분이 수행능력 70이상이었다. 50세 이상인 경우 26명이었고 50세 이하인 경우가 18명이었다. 환자의 중앙연령은 52.5세이고, 범위는 2에서 78세였다. 방사선 치료는 1989년 1월부터 1991년 12월까지 단순분할 방사선이 19명의 환자에게 시행되었고 1992년 1월부터 1993년 1월까지 24명의 환자에서는 다분할 방사선 치료가 시행되었다. 단순분할 방사선치료는 종양부위에 하루 일회 1.8Gy씩 조사되어 7주에 걸쳐 총 63Gy가 조사되었다. 그리고 다분할 방사선 치료는 종양 부위에 1.6Gy씩 1일 6시간 간격으로 2회씩 조사하여 4주에 걸쳐 총 64Gy가 조사되었다. 중앙추적 관찰기간은 9개월이었고 범위는 7개월부터 4년이었다. 전체 환자의 중앙생존 기간은 9개월 이었고 단순분할 방사선 치료군과 다분할 방사선 치료군에서 각각 9개월, 10개월 다형성교아종과 악성성상 세포종에서 각각 10개월 9.5개월이었다. 방사선 조사방법에 따른 비교와 조직학적 형태에 따른 비교에서 의미있는 통계적 차이는 발견할 수 없었다. 컴퓨터 단층촬영이나 핵자기 공명촬영으로 추적 관찰이 가능했던 36명의 환자에서 질병의 상태를 평가하였으며 다분할 방사선 치료군에서 21명중 4명이 무병상태로 생존해 있었고 단순분할 방사선 치료군에서는 13명중 무병상태로 생존한 환자는 없었다. 20명의 환자에서 질병이 진행되거나 재발하였는데 이들중 8명은 방사선이 조사되지 않은 새로운 부위에서 재발하였다. 본 연구에서는 일반적으로 예후 인자로 알려진 연령, 수행능력, 조직학적 형태, 종양의 절제정도가 예후에 영향 미치는 지를 확인할 수 없었다.

본 연구에서 추적기간이 짧기 때문에 정확한 결론을 도출하기 어려우나 고등급 교종에서 다분할 방사선 치료 방법으로 1.6Gy씩 1일 2회로 총 64Gy 조사는 단순분할 방사선 치료방법에 의한 결과보다 더 나은 결과를 보여주지는 못하였다. 그러나 단순분할 방사선 치료와 비교해서 치료에 큰 장애 없이 치료기간을 약 3주 정도 단축시킬 수 있었다. 정확한 결론을 얻기위해 지속적인 추적관찰이 필요하며 치료결과를 향상시키기 위하여 방사선 조사 방법에 있어서 총 방사선량, 1회 방사선 조사량의 조정을 고려한 연구가 필요하며 총 방사선량을 증가시키는 한 방법으로 다분할 방사선 치료와 감마 나이프나 침입형 근접치료를 병용하는 방법도 고려될 수 있겠다.