REVIEW PAPER

RADIATION THERAPY IN THE MANAGEMENT OF MALIGNANT GLIOMAS

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SUMMARY

Key words : radiotherapy, malignant gliomas
Several randomized trials have provided evidence supporting the efficacy of conventional radiation therapy in the management of malignant gliomas. In this paper a review of different radiotherapeutic modalities including non conventional regiments of irradiation, use of radiosensitizers, boron neutron capture therapy, stereotactic radiosurgery and brachytherapy is presented.

INTRODUCTION

High grade (III and IV) malignant gliomas are the most common primary brain tumours in adults. It is a devastating illness : cures are rare and more than 50% of patients die within 12 months. The median survival time for patients with anaplastic astrocytoma is 36 months, and for patients with glioblastoma multiforme, who make up 80% of those accrued to cooperative group studies is 10 months, whereas the 3-year survival rate is only 6% (Leibel et al. 1994).
Standard treatment for malignant gliomas begins with surgical intervention followed by irradiation. The role of chemotherapy remains controversial (Graham 1993). For reasons which are not clear, malignant gliomas do not metastasize to distant organs except very rarely, and the pattern of failure is local tumour recurrence. Unfortunately, the method to overcome this resistance to local treatment is not known. Various means have been tried to improve the effectiveness of radiation therapy. Such attempts include the use of non conventional regimens of irradiation, neutron therapy, radiation sensitizers, stereotactic external beam irradiation and interstitial brachytherapy.

TOTAL DOSE AND TREATMENT VOLUME

Salazar et al. (1979) have presented the use of unusually high doses of irradiation in patients suffering from malignant gliomas. Compared with a conventional dose (50 Gy), his treatment with up to 75-80 Gy produced an increased survival for both grade III and IV patients, but the gain was limited and only maintained for two years in grade IV gliomas, and for four years in grade III. Walker et al. (1979) have reported a significant relationship between dose and survival in 621 patients with malignant gliomas : the greater the dose, the greater median survival (MS). The MS for patients treated with the dose of 50 Gy and 60 Gy were respectively 7 months and 11 months, but this difference was upheld for only a limited time of two years. A retrospective analysis of 178 patients presented by Shibamoto et al. (1990) showed that the radiation dose did not appear to influence significantly long term survival.

The widely infiltrating nature of high grade gliomas has encouraged radiotherapists to treat large tissue volumes (Bloom 1982), but since failure in these tumours is invariably a result of recurrence in the primary site, the value of routine whole brain irradiation is questionable (Hess et al. 1994, Shapiro et al. 1989).

UNCONVENTIONAL IRRADIATION

Due to the disappointing results with conventional radiation therapy, different treatment alternatives have been explored. Multiple daily fractions have been used in attempt to increase tumour control and spare normal tissues. Hyperfractionation consists in giving multiple daily fractions in smaller than conventional doses, but reaching a therapeutic dose in a treatment period similar to conventional schedules. Accelerated fractionation involves giving 2 or 3 doses per day to a therapeutic dose resulting in a short overall treatment time. The theoretical advantages of using multiple daily fractions are alpha type cell killing, slow tumour repopulation, and enhancement of normal tissue tolerance (Thames et al. 1983). Results of postoperative

multiple daily fractionated radiation therapy are presented in table 1.

Majority of patients with malignant gliomas die of progressive disease, largely palliative treatment should be considered for them. Every such treatment for poor prognosis patients must be able to demonstrate effectiveness in terms of palliation and should be short, well tolerated, non-toxic as well as acceptable to patients and careers. In this view, several studies of hypofractionated irradiation were proposed, and their results are summarized in table 2.

Author	No of patients	Fractionation schedule	MST (months)
Douglas et al. 1982	30	AF	10,5
Payne et al. 1982	78	HF	12
Shin et al. 1983	35	HF	13
Keim et al. 1987	38	AF	9
Bignardi et al. 1987	73	HF	12,5
Ludgate et al. 1988	42	AF	11,5
Hernandez et al. 1990	14	AF	10,5
Shenounda et al. 1991	39	AF	14,2
Nelson et al. 1993	141	HF	13,4
Gonzalez et al. 1994	66	AF	8,9

AF : accelerated fractionation
HF : hyperfractionation
MST : mean survival time

TABLE 1. Results of postoperative multiple daily fractionated radiation therapy of malignant gliomas.

Author	No of patients	Fractional dose (Gy)	MST (months)
Kapp et al. 1982	19	6	9,4
Maire et al. 1987	42	3	10
Hercbergs et al. 1989	28	6	8
Marcial-Vega et al. 1989	20	3	12
Tamura et al. 1989	24	5	10
Sautter-Bihl et al. 1991	41	3,5	11
Thomas et al. 1994	32	3	9
Slotman et al. 1996	30	3	9
Gliński et al. 1998	59	4	13

TABLE 2. Results of postoperative hypofractionated radiation
therapy of malignant gliomas.

RADIOSENSITIZERS

Relative radioresistance of malignant gliomas is believed to be associated with the presence of hypoxic potentially viable tumor cells. Clinical efforts to sterilize these „radioresistant" cells have focused on radiation using hyperbaric oxygen, radiosensitizers such as electron affinic drugs (metronidazole, misonidazole), halogenated deoxyuridines (iododeoxyuridine, bromodeoxyuridine) and high linear energy transfer radiation (Chang et al. 1977, Urtasun et al. 1976, Bleehen et al. 1981, Jackson et al. 1987, Catteral et al. 1980, Castro et al. 1997, Pickles et al. 1997). Of all clinical studies with the objective to reduce the hypoxic tumour cells compartment in malignant gliomas, there is no evidence that the measures taken to minimise the hypoxia had the desired effect. This has necessitated the search for new treatment approaches such as radiotherapy combined with carbogen breathing and nicotynamide (in experimental models breathing carbogen prior to, and during irradiation helps to re-oxygenate chronically hypoxic cells, and nicotynamide has the ability to reduce acute hypoxia).
Unfortunately these studies have met with little success (Van der Maazen et al. 1995, Rojas et al. 1992).

BORON NEUTRON CAPTURE THERAPY (BNCT)

BNCT is a binary treatment (the basic concept is to selectively destroy malignant cells while concomitantly sparing normal tissue) of high grade gliomas that involves incorporating ^{10}B into the tumour using appropriate pharmacological agents and then irradiating the tumour with termal or epitermal neutron beams (Laramore et al. 1996). One hundred twenty patients with intracranial tumours and one patient with extracranial nerve related tumour were treated by standard technique of BNTC using ^{10}B - sodium-mercaptoundecahydrodecarbonate. Nine patients have lived longer than 10 years. It can be suggested that BNTC is a radiotherapy that can produce „cure" of both malignant and benign brain tumours while preserving a good quality of life if conducted without conventional irradiation (Hatanaka et al. 1994).

STEREOTACTIC RADIOSURGERY

Stereotactic radiosurgery has historically been used for arteriovenous malformations and benign tumours, but have recently been upheld as a tool in the multimodality management of intracranial malignancies. In selected patients with small, relatively spherical high grade gliomas, radiosurgery appears to produce tumuor control, survival, and toxicity similar to that of brachytherapy (Flickinger et al. 1994). A total of 115 patients were treated with a combination of surgery, external beam radiation therapy, and linac-based radiosurgery. The actuarial 2-year and median survival for all patients analyzed was 45% and 96 weeks, respectively. In comparison with the results from a previously published analysis of 1578 patients entered on three RTOG external beam radiation protocols, those patients treated with radiosurgery had a significantly improved 2-year and median survival (Sarkaria et al. 1995).

BRACHYTHERAPY

The rationale for the brain implant is that interstitial irradiation can deliver a large dose to the tumour volume while sparing surrounding normal tissues. Unfortunately, only 20-30% of patients are eligible to receive implantation on the size and disposition at the tumour as well as the general condition of the patient (Loeffler et al. 1990). Since the early 1950s the effect of brachytherapy on intracranial tumours by direct interstitial or intracavitary implanting of radioactive isotopes could first be demonstrated only in small volume tumours or cysts : in some cases the effect was even curative. This therapy has only become possible by using stereotactic operations methods. A total of 307 patients with glioma were treated with high-activity removable iodine-125 interstitial brain implants at the UCSF. Recurrent gliomas underwent brain implant alone, whereas previously untreated tumours underwent brain implant after external beam radiotherapy. Of these patients, 106 had primary and 67 had recurrent glioblastoma multiforme. Median survival time for those patients was 22 months and 12 months respectively. This study demonstrates that interstitial implant is well-tolerated and prolongs survival in patients with primary and recurrent gliobastoma, as evidenced by the 3-year survival rates of 22% and 15%, respectively (Scharfen et al. 1992).

CONCLUSIONS

Malignant gliomas are essentially localized tumours that have defied most treatment. Surgical resection results in a median survival of six months, postoperative conventional irradiation may increase survival by as much as 100%. Evidence of improvement in survival was observed neither in patients receiving multiple daily fractionated irradiation, nor in patients for whom radiation sensitizers such as nitroimidazole compounds or halogenated pyrymidine analogs were associated to radiation therapy.

Hypofractionated schedules have a rather palliative role in the management of malignant gliomas.

Combination of full-dose external beam radiotherapy and brachytherapy or radiosurgery boost in selected patients with malignant gliomas leads to an increase in median survival, while external beam irradiation alone in patients with similar prognosis does not.

No therapeutically beneficial effect of high linear energy transfer irradiation was observed.

It is evident that malignant gliomas cannot be eradicated by presently available radiotherapeutic techniques, and still present a supreme challenge to local modes of therapy.

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