TWICE A DAY ACCELERATED IRRADIATION IN POSTOPERATIVE TREATMENT OF SUPRATENTORIAL GRADE III AND IV ASTROCYTOMAS IN ADULTS.

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ABSTRACT

Fourty-seven patients with histologically proven grade III-IV astrocytoma received postoperative accelerated radiotherapy with 2 fractions of 2,65 Gy twice daily, up to total tumor dose of 53 Gy in ten days. The tolerance of the treatment was good, actuarial survival rates at 2, 3 and 5 years were 15%, 9% and 0% respectively.

INTRODUCTION

High grade astrocytomas account for 40% of all central nervous system malignancies in adults (Choi et al., 1970). The surgical intervention in these highly malignant lesions is unlikely to be curative, and because of their lesions' diffused spread continues to be unsatisfactory. Postoperative irradiation may increase survival by as much as 100%, but the prognosis of anaplastic astrocytomas is still one of the most serious problems in oncology (Leibel et al, 1994).

The objective of this study is to evaluate the efficacy of postoperative Twice Daily Accelerated Irradiation (TDAI) of patients with grade III and IV astrocytomas.

MATERIAL AND METHODES

The population for the study was derived from neurosurgical centers which referred patients to the Maria Skłodowska-Curie Memorial Center in Kraków for radiation therapy. Surgery consisted of as complete tumor removal as possible. All surgical specimens were evaluated by the same pathologist, according to the classification, as described by Kernohan (Kernohan-Sayre, 1952). Grade III astrocytomas have malignant cytologic feature, including mitoses and hyperchromatic nuclei, and in the grade IV neoplasms, there are significant amounts of necrosis hemorrhage and marked variation in cell size and detail. Between 1989 and 1993, 47 adult patients with a histologically confirmed diagnosis of astrocytoma grade III-IV, received postoperative TDAI. Patients were treated with 2,65 Gy per fraction, twice daily with a 6 hour interval between fractions up to the total dose of 53 Gy over 12 days. The targed volume (based on pre- and postoperative CT scans) encompassed the known tumour-bearing area plus three centimeters of surrounding tissue. The distribution of patient characteristics is given in Table I.

Table I. Patient characteristics.

Characteristics	No of patients	(%)
Gender:		
Male	27	(57%)
Female	20	(43%)
Age (years):		
40 and less	19	(40%)
More than 40	28	(60%)
Tumor location:		
Frontal	16	(34%)
Temporal	16	(34%)
Parietal	9	(19%)
Occipital	6	(13%)
Surgery:		
Total resection	9	(19%)
Partial resection	38	(81%)
Histology:		
Astrocytoma III	14	(30%)
Astrocytoma IV	33	(70%)
Karnofsky's index:		
60% and more	28	(60%)
Less than 60%	19	(40%)

SUPPORTIVE TREATMENT

Systemic anticonvulsants (phenytoin or phenobarbital) were administrated to all patients during irradiation. Dexamethasone was given in a dose of 12-24 mg/day, only as symptomatic medication required to control cerebral edema.

FOLLOW-UP

Patients were checked every 4 months after completion of therapy. Physical and neurological examination were done, and a CT scan of the brain at each follow-up visit was obtained.

STATISTICAL CONSIDERATION

The lenght of survival was measured from the day of surgery and estimates of the survival were obtained by the product-limit method (Kaplan-Meier, 1958). At the time of this analysis 42 of 47 patients were known to have died.

RESULTS

The treatment was generally well tolerated, signs and symptoms of increassed intracranial pressure occured in 4 patients. Of the 47 patients treated with TDAI, six showed improvement in their Karnofsky's performance status (KPS). This improvement was usually evident at the beginning of the second week of irradiation. No change in KPS was observed in 41 patients. The probability of survival of 47 patients treated with TDAI is given in Table II.

Table II. Actuarial survival of 47 patients with grade III, IV astrocytomas.

Survival	Probability
2-years	0,15
3-years	0,09
4-years	0,05
5-years	-

DISCUSSION

Anaplastic astrocytoma present a supreme challenge to local modes of therapy. These tumours are not curable by currently available postoperative radiotherapeutic techniques. In an attempt to improve the therapeutic ratio, non conventional fractionation schedules have been proposed in many centers. Different studies have employed increased fractional dose or decreased treatment time, both of which lead to an increased biologically effective dose, but have failed to demonstrate improved long-term survival. Table III and IV present the results of postoperative irradiation of anaplastic astrocytomas according to different regimens of fractionation. Optimum parameters of dose, volume and type of fractionation are not defined for the treatment of high grade astrocytomas with external beam radiotherapy, but in spite of all considerable limitations, radiotherapy remains the most effective treatment at our disposal for affecting the course of these tumors. Postoperative irradiation plays a palliative role in the management of anaplastic astrocytomas, so we believe that this treatment should be of short duration and the fewest side-effects. Therefore our TDAI regimen is worth recommendation.

Although there were no radiation related late toxicities in this study, the late effects of large incremental fractions on normal brain tissue can be potentially severe. The true incidence of brain necrosis in our series is difficult to determine. The reason for this difficulty includes short survival of patients with malignant astrocytomas and, therefore the insufficient time interval for necrosis to develop. Necrosis, if it occures, usually does from 6 to 22 months after the completion of radiotherapy (Marks et al., 1981).

Table III. Results of postoperative hypofractionated irradiation of anaplastic astrocytomas.

Author	Fraction size (cGy)	2-years survival	5-years survival
(Hercbergs et al., 1989)	600	15%	-
(Marcial-Vega et al., 1989)	300	19%	-
(Tamura et al., 1989)	500	26%	-
(Thomas et al., 1994)	500	14%	-

Table IV. Results of postoperative multiple daily fractionated irradiation of anaplastic astrocytomas.

Author	Fraction size (cGy)	2-years survival	5-years survival
(Gonzalez et al., 1994)	200	8%	-
(Hernandez et al., 1990)	100	7%	-
(Keim et al., 1987)	160	10%	-
(Ludgate et al., 1988)	76	17%	-

REFERENCES:

Bloom HJG. Intracranial tumors: responce and resistance to therapeutic endeavors, 1970-1980. Int J Radiat Oncol Biol Phys 8: 1083-1113, 1982

Choi N, Schuman L, Gullen WM. Epidemiology of primary central nervous system neoplasms. Am J Epidemiology 91: 467-485, 1970fractionation radiotherapy for hospitalized glioblastoma multiforme patients with poor prognostic factors. J Neurooncol 9: 41-45, 1990

Gonzalez D, Mertens J, Bosch DA et al. Accelerated radiotherapy in glioblastomas: a dose searching prospective study. Radiother Oncol 32: 98-105, 1994

Hercbergs AA, Tadmor R, Findler G et al. Hypofractionated radiation therapy and concurrent cisplatin in malignant cerebral gliomas. Rapid palliation in low performance status patients. Cancer 64: 816-820, 1989

Hernandez JC, Maruyama Y, Chin HW. Accelerated Kaplan ME, Meier P. Non parametric estimation from incomplete observation. J Am Stat Assoc 53: 457-481, 1958

Keim H, Potthoff PC, Schmidt K et al. Survival and quality of life after continous accelerated radiotherapy of glioblastomas. Radiother Oncol 9: 21-26, 1987

Kernohan JW, Sayre GP. Tumors of the central nervous system. In: Atlas of tumor pathology, sec 10, fasc no 35 and 37. Armed Forces Institute of Pathology, Washington DC, 1952, 22-24

Ludgate CH, Douglas B, Dixon PF et al. Superfractionation radiotherapy in grade III, IV intracranial gliomas. Int J Radiat Oncol Biol Phys 15: 1091-1095, 1988

Marcial-Vega VA, Wharam DM, Leibel S et al. Treatment of supratentorial high-grade gliomas with split course high fractional dose post-operative radiotherapy. Int J Radiat Oncol Biol Phys 16: 1419-1424, 1989

Tamura H, Nakamura M, Kumimine H, Ono H. Large dose fraction radiotherapy in the treatment of glioblastoma. J Neurooncol 7: 113-119, 1989

Thomas R, James N, Guerrero D et al. Hypofractionated radiotherapy as palliative treatment in poor prognosis patients with high-grade glioma. Radiother Oncol 33: 113-116, 1994