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SURVIVAL IN PATIENTS WITH MALIGNANT GLIOMAS OF THE BRAIN

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ABSTRACT

The present retrospective study was designed to analyze factors with prognostic values a) within, and b) significantly associated with, short-term (12 months or less) and long-term (more than 24 months) survival times, in 72 consecutive patients treated for malignant gliomas. Among 41 (57%) short-term surviving patients, the absence of both aphasia and motor deficit (as initial presenting symptoms), postoperative radiation therapy alone or in combination with chemotherapy, and reoperation were associated with a relatively better survival prognosis. Among 15 (20.8%) long-term surviving patients, postoperative radiation therapy and anaplastic, as histological type of astrocytoma, were marginally associated with improved survival time. The addition of conventional chemotherapy to postoperative radiation therapy failed to show a significant improvement in survival time in both survival groups. The long-term survival was significantly associated with the following factors: age (under 51 years), reoperation and the absence of lymphocyte infiltration.

A satisfactory quality and duration of survival was achieved in a minority of patients with malignant gliomas. Furthermore, a more appropriate postoperative antitumor therapy may increase the number of these patients, by avoiding fatal injuries to the normal brain tissues induced by postoperative antitumor therapies.

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INTRODUCTION

Until the last decade, the usual prognosis in patients harboring malignant gliomas of the brain was a mean survival time not exceeding 10 to 12 months after the best conventional therapy and a fatal outcome in all cases. Recent advances in diagnostic and surgical techniques[10,28] and progress in postoperative therapies[17,24,32] including reoperation, [6,26,28,35] have led to some encouraging improvement in the length and quality of survival in patients with malignant gliomas.

At this stage of progress in neuro-oncology, it would perhaps be appropriate to reexamine the prognostic factors apparently and/or statistically associated with a short (12 months or less) or a relatively long (more than 24 months) survival time in patients harboring malignant gliomas. Several studies, designed to evaluate the relative values of prognostic factors in patients with malignant gliomas are available. [6,8,11,26,28,34,35] However, we felt that a study in which the two extreme survival groups of patients are separately analyzed and compared might help us to obtain a better prediction for the prognosis of any given patient with a malignant glioma. Moreover, such an analysis may provide additional insight to enable an increasing number of patients to pass into the long-term surviving group.

The purpose of this non-randomized retrospective study is: first, to analyze prognostic factors most often associated with a short-term (12 months or less) or a

long-term (more than 24 months) survival time; and second, to compare the association of these factors between the two survival groups. Factors considered in this study were: age, sex, location of tumor, initial presenting symptoms, preoperative symptomatic interval, reoperation, extent of tumor removal, histological subtype of tumor, round cell (lymphocyte) infiltration in the surgical specimen and therapy.

PATIENTS AND METHODS

The study was carried out on a non-randomized series of 72 consecutive patients with histologically proven malignant glial tumors. All patients included in this series had undergone diagnostic and therapeutic craniotomy, radiation and antitumor drug therapy by the same anesthetic, surgical, and oncological teams over a period of 11 years ending in June, 1985. No needle biopsy was performed in these groups of patients.

Among our patients with malignant gliomas, 41 (57%) survived 12 months or less (short-term survival), 16 (22.2%) survived more than 12 and less than 24 months, and 15 (20.8%) survived more than 24 months (long-term survival).

All patients included in the present study had a complete clinical record and at least one pathological slide of the surgical specimen available for review. All neuropathological slides were reviewed by the author, without knowledge of clinical data, and reassessed in using the current classification system for malignant gliomas of the brain[18,19]. The two histological subtypes included in this study are: anaplastic astrocytomas and glioblastomas muliforme.

Patients with histologically proven malignant gliomas were eligible for this study only if the postoperative survival time was longer than three weeks (i.e. we excluded the immediate postoperative mortalities), and if a complete medical chart, follow-up and pathological slides were available.

Survival time was defined as being the time span between the initial operation and the time of death, or closest to the completion of this study (censored data).

Radiation and chemotherapy

All radiation used was in megovoltage. Two radiation therapy schedules were used. In the first, 45 to 60 Grays (Gy) were delivered at a daily dose of 1.8 to 3 Gy and three to five times a week; two-thirds of the total dose of radiation was alternately delivered to the whole brain through lateral parallel opposed fields, and one-third (boost) to the tumor site. In the second, a total dose of 34 Gy was scheduled as 8.5 Gy delivered on days 1,3,21 and 23 (split-course therapy); the whole brain was exposed to 17 Gy, and 17 Gy (boost) was delivered to the tumor site.[22,25]

Antitumor chemotherapy consisted in the per oral administration of 1-(2-chloroethyl). 3-cyclohexyl-1-nitrosourea (CCNU) or intravenous administration of 1,3-bis (2-chloroetheyl)-1-nitrosourea (BCNU) (80-110 mg/m^2 every 6-8 weeks) at least 4 weeks after completion of radiation therapy.

All patients included in this study harbored a supratentorial hemispheric malignant glioma. These tumors were divided into two groups; anaplastic astrocytoma, and glioblastoma multiforme. Other malignant glial tumors such as malignant ependymomas or cerebral gangliogliomas were excluded.

Lymphocyte infiltration was defined as the existence of at least a cluster of five lymphocytes (or mononucler cells morphologically consistent with lymphoreticular origin) in a perivascular or non-perivascular distribution.[23]

Statistical analyses

The chi-square test was used to evaluate the statistical significance of dependence of variables between the two survival groups of patients. The t-test was used to evaluate the statistical significance of dependence of variables upon survival time within each survival group of patients. The p-value has been used as an indicator of the level of statistical significance. Whenever a variable of small size (less than 5) was to be tested, the Yates rule to correct the p-value for small numbers was applied. Marginally significant, significant, and highly significant associations are defined as p-values of more than 0.05 and less than 0.10, between 0.05 to 0.01, and less than 0.01, respectively.

RESULTS

SHORT-TERM SURVIVING PATIENTS (12 MONTHS OR LESS)

41 patients (57%) survived 12 months or less.

Age, sex and survival time

The median and mean ages of patients were 61 and 58.4 (SD: 13.06) years, ranging from 17 to 78 years of age. Approximately three-quarters of the patients (73.2%) were males.

The median and mean survival times for short-term surviving patients were 7 and 6.7 (SD: 3.47) months, respectively. Close to one-half (48.6%) of patients (35 patients) survived 6 months or less.

Initial presenting symptoms

Headache was the most frequent initial presenting symptom in 75.6% of patients, and it was more com-

mon among patients younger than 50 years of age (89%). 63.4% of patients in this group of survival were free of seizure and 73.2% of patients did not have speech disorder. Motor deficit and sensory loss, as initial presenting symptoms, were observed in 46.3% and 17.1% of patients respectively. Fifteen patients (36.6%) were free of motor or sensory symptoms at the time of diagnosis of their tumor.

Interval of Time Between First Symptom And The Initial Operation

Median and mean intervals of time between the initial presenting symptom and the initial operation were 3 and 14.4 (SD: 43.05) months, respectively, ranging from 1 to 240 months.

Location of Tumor

53.7% of patients had a tumor located on the right side of the brain, and 46.3% of patients had a tumor located on the left. The most common site of tumor was in the temporal lobe in 41.5% of patients, followed by frontal lobe in 31.7% of patients, occipital lobe in 14.6% of patients and parietal lobe in 12.2% of patients.

Therapy

Five patients (12.2%) underwent surgery alone, 19 patients (46.3%) received postoperative radiation therapy, and 17 patients (41.5%) received postoperative radiation and chemotherapies.

Amount of Tumor Removal And Reoperation

The tumor was partially removed in 30 (73.2%) patients and complete removal of tumor was achieved in 11 (26.8%) patients. The extent of tumor removal was judged during the operation.

Only 4 patients (9.8%) with short-term survival had undergone a second operation. The median and mean intervals of time between the initial and the second operations were 6 and 8.6 (SD: 0.07) months, respectively.

Lymphocyte Infiltration

Lymphocyte infiltration was present in the biopsy specimens of 23 (56.1%) patients.

Histological Type Of Tumor

Eleven patients (26.8%) harbored anaplastic astrocytomas, and 30 patients (73.2%) harbored a glioblastoma multiforme.

As initial presenting symptoms, aphasia was significantly, and motor deficit was marginally, associated with a poorer prognosis among short-term surviving patients. Postoperative radiation therapy or a combination of radiation and chemotherapy significantly improved the prognosis. Reoperation was strongly associated with improved prognosis, in this survival group (Table I).

TABLE I.

FACTORS SIGNIFICANTLY ASSOCIATED WITH A RELATIVELY LONGER SURVIVAL TIME AMONG SHORT-TERM SURVIVING PATIENTS.

	p-VALUE
Absence of Aphasia	0.02
Radiotherapy	0.007
Radiation and Chemotherapy	0.005
Reoperation	0.001

Long-Term Surviving Patients (More Than 24 Months)

Fifteen patients (20.8%) survived more than 24 months.

Age, Sex And Surival Time

The median and mean ages of patients were 41 and 42.8 (SD: 10.5) years, ranging from 22 to 65 years of age. Two-thirds of patients (66.6%) were males.

The median and mean survival times for long-term surviving patients were 39 and 57.3 (SD: 34.62) months, respectively (minimum 27 months and maximum 128 months). One-third (5 patients) of long-term surviving patients, survived longer than 64 months (5.3 years).

Initial presenting symptoms

Headache was the most frequent initial presenting symptom in 12 (80%) patients, and it tended to occur predominantly (90%) in patients younger than 50 years of age. The absence of both seizure and aphasia was noted in 66.6% and 60% of patients, respectively. Motor deficit and sensory loss, as initial presenting symptoms, were uncommon and occurred in 33.3% and 13.3% of patients respectively. Eight patients (53.3%) were free of motor or sensory symptoms.

Interval of time between first symptom and initial operation

Median and mean intervals of time between the initial presenting symptom and the initial operation were 3 and 38.2 (SD: 73.35) months, respectively, ranging from 1 to 264 months.

TABLE II.

FACTORS SIGNIFICANTLY ASSOCIATED WITH SHORT-TERM OR LONG-TERM SURVIVING PATIENTS.

	SHORT-TERM	LONG-TERM	P-VALUE
Age	Above 50 yrs	Under 50 yrs	0.001
Reoperation	No	Yes	0.001
Lymphocyte	Present	Absent	0.05

Location of tumor

The tumor was predominantly located on the left side (in 66.6% of patients) of the brain. The most common site of the tumor was in the parietal lobe in 33.3% of patients, followed by the frontal lobe in 26.6% of patients. Temporal and occipital lobes were equally the site of tumors in 20% of patients for each lobe.

Therapy

All patients received postoperative radiation therapy, and 7 patients (46.6%) received chemotherapy in addition.

Amount of Tumor removal and reoperation

Partial removal of the tumor was achieved in 9 (60%) patients and total excision of the tumor was performed in 6 (40%) patients.

Sixty percent of patients with long-term survival were reoperated upon. The median and mean intervals of time between the initial and the second operation were 25 and 29.8 (SD: 17.39) months, respectively.

Lymphocyte infiltration

Lymphocyte infiltration was absent in the biopsy specimens of 12 (80%) patients.

Histological type of tumor

Eight patients (53.3%) harbored an anaplastic astrocytoma, and 7 patients (46. 7%) harbored a glioblastoma multiforme.

OUTCOME OF LONG-TERM SURVIVING PATIENTS

Among our 15 long-term surviving patients, 3 were lost to follow-up, 22, 39 and 43 months after the initial operation (the dates of death were obtained through referring physicians).

One of the long-term surviving patients is still alive and professionally active at 116 months (9.7 years) after the initial craniotomy for total removal of a glioblastoma multiforme, located in the left parietal lobe. Headaches were the only initial presenting symptom lasting for 3 months prior to the diagnosis of her brain tumor. She had received postoperative radiation and chemotherapy, and underwent a second operation 67 months after the initial craniotomy. The biopsy specimen of this patient was free of tissue lymphocyte infiltration. This lady is now 47 years old, and is continuing to take care of her family and teaching in a primary school. The last computed tomography scan performed in March 1984 did not show recurrence of the tumor and ventricular sizes were within normal limits.

Two patients stopped their professional activities 10 and 11 months after surgery, but they were able to lead normal lives until 6 to 8 weeks before death.

Five patients were able to resume their previous professional activities until 2 to 4 months before death. One of these 5 patients required (13 months after the initial operation) a medium pressure ventriculo-peritoneal shunt which proved to be helpful.

Two patients with a severe degree of neurological disturbance had to be kept at home and needed help to feed and dress themselves and for ambulation.

One patient could resume almost 75% of his professional activities 6 months after the initial operation. Sixteen months after the initial operation (13 months after completion of radiation therapy), he developed a progressive memory loss, followed by cognitive disorders and personality changes. A computed tomography scan performed at this time showed a hypodense lesion on the left parietal region (site of the removed tumor) without evidence of recurrence of the tumor, and both lateral ventricles were slightly enlarged. A medium pressure ventriculo-peritoneal shunting system was then placed. The shunting procedure resulted in temporary and partial improvement of his symptoms, however, further aggravation of his clinical state led to dementia, apparently unrelated to tumor regrowth. The conventional intravenous BCNU chemotherapy was discontiued after 5 courses (cumulative dose: 810 mg), and the administration of Dexamethasone did not improve his clinical symptoms. This patient died 27 months after the initial operation. Radiation induced lesion of the brain was the most probable cause of death in this case.

Another patient began, 33 months after the initial craniotomy and 30 months after completion of radiation therapy, to develop a progressive right side hemiparesis, personality changes and symptoms related to cerebellum and brain stem dysfunction. The computed tomography scan showed a heterogenous cystic lesion on the left parietal lobe (site of the removed tumor), a hyperdense and homogenous lesion on the right frontal paraventricular region, and a hyperdense and homogenous lesion located in the anterior and medial part of the cerebellum. All antitumor therapies were rejected by the family; supportive and Dexamethasone therapies were then maintained until death. Further neurological aggravation led to a vegetative state during the last two months of his life, and he died 36 months after the initial operation. The clinical diagnosis evoked before death was multiple metastases of his glioblastoma multiforme through cerebrospinal pathways. The post-mortem examination of this patient revealed that the two hemispheric lesions were typical radiation necrotic lesions with only a minimal recurrence of the tumor on the site of original tumor (left

parietal lobe). the cerebellar lesion was composed of a large (metastatic) malignant glioma surrounded by a strip of necrotic (coagulative) tissue, which had invaded the right part of lower pons.

The perilesional in farcted lesion was more compatible with radiation induced necrosis than peritumoral infarcted tissue.[21,22,30,31]

DISCUSSION

In this relatively small series of non-randomized patients, the analysis of their censored data reveals that approximately 21% of patients with malignant gliomas survived more than two years. This rate of survival in patients with malignant gliomas is slightly better than that of similar studies (mostly concerning glioblastomas multiforme) recently reported.[5,6,12,20,27,28,33] In a previous study[26], we observed, in agreement with most series of the literature, the unquestionable effectiveness of postoperative radiation therapy alone or in association with chemotherapy upon survival time.[11,14,26,28,32,34] However, in both survival groups, the addition of chemotherapy to the postoperative radiation therapy, has failed to show a significant improvement in survival time of patients. This finding is inclined to be in contrast to reports favouring chemotherapy[9,17,32] and is less pejorative towards the effectiveness of conventional chemotherapy than the results in reported series that have rebuffed the effectiveness of conventional chemotherapy.[24,33]

In comparing the two groups of survivors, age, reoperation and the presence of tissular lymphocyte infiltration in surgical specimens of patients were the only variables to have a significant (strong) association with short-term or long-term survival groups (TableII). Among patients with malignant gliomas, the probability for patients younger than 50 years of age to be within the long-term survivor group, was found to be significantly high; and the outcome of patients older than 50 years tended to be strongly associated with short-term survival.

A significant number of long-term surviving patients were reoperated upon; this finding implies that attempts should be made to reoperate upon patients with recurrent malignant gliomas, and perhaps to enlarge the indication of reoperation in case of recurrence of malignant gliomas, all the more so as the reoperation is the only factor out of these three (age, reoperation and tissular lymphocyte infiltration), with a significant prognostic value, that can be managed by neurosurgery, to provide patients with a better chance of a longer survival.

The presence of tissular lymphocyte infiltration in biopsy specimens of patients harboring malignant gliomas was strongly associated with short-term survival. The role played by tissular lymphocytes in biopsy specimens of patients with malignant gliomas remains so far mysterious and requires further investigation.[7,13,23]

Although the number of long-term surviving patients with malignant gliomas is limited, we may be increasingly optimistic about long-term survival in these patients.[3,9,24,26,28] It implies that solemn attempts should be made in using every possible means, to pass an increasing number of patients with malignant gliomas into the long-term surviving group, and to prolong the survival time of this group of patients. The two factors with significant prognostic values which can be handled by the neurosurgeon and his collaborators are reoperation and postoperative chemotherapy. The latter may be, in certain circumstances, a real dilemma. The tendancy is to be as aggressive as possible toward malignancies; however, in long-term survivors, fatal complications of our treatments are now more frequently observed, even when the growth of the treated malignant lesion has been controlled, all the more so as, the survival time of patients with malignancies of the brain is likely to be further prolonged. Parallel to the progress on brain tumors[2,4,10], research on more appropriate postoperative radiation and chemotherapy schedules may help to improve our therapy performances.[1,15,16,22,25,29]

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