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PROGNOSTIC FACTORS IN MALIGNANT GLIOMAS WITH SPECIAL REFERENCE TO INTRA-ARTERIAL CHEMOTHERAPY

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Survival was analyzed in 173 patients with malignant gliomas to study the importance of possible pretreatment prognostic factors. Seventy-nine of these patients received preirradiation intra-arterial chemotherapy with BCNU combined with vincristine intravenously and procarbazine orally; the others received only postoperative whole-brain irradiation. To judge by univariate and multivariate analyses the most important pretreatment prognostic factors were histology, corticosteroid dependency, pretreatment performance status and frontal lobe location of the tumors. Patients with anaplastic astrocytoma, not corticosteroid-dependent, with pretreatment performance status of 0–2 and with a frontal lobe location of the tumor seemed to benefit most from preirradiation chemotherapy.

The results of treatment of patients with high-grade malignant gliomas are poor with, at best, a median survival of approximately 9 months, and a 2-year survival rate of 5–10% (1, 2). Prospective randomized studies have confirmed some benefit of postoperative radiotherapy (3–5). Adjuvant chemotherapy has not yet a clearly proven value but seems to lead to an increased number of long-term survivors (6).

Several groups have analyzed the influence of various prognostic variables on patient survival. The most important factors were age, performance status and tumor grade (7–9). The identification of groups of patients with favorable or unfavorable prognostic factors could be of value for decisions on treatment.

In the present paper we report on an analysis of the influence of some possible prognostic factors on survival. Two postoperative treatment protocols were employed. In the first protocol postoperative preirradiation chemotherapy was studied while the second protocol represented a retrospective study of postoperative radiotherapy alone (10). Survival in relation to the possible prognostic factors was studied by univariable and multivariable methods.

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Material and Methods

In the first study ('chemotherapy group') patients with malignant gliomas (anaplastic astrocytoma and glioblastoma multiform) received 4 cycles of chemotherapy after operation and before irradiation. The chemotherapy consisted of 4 monthly intracarotid infusions of 160 mg BCNU combined with 2 mg vincristine i.v. and procarbazine orally. If tumor progression occurred during chemotherapy, irradiation was started immediately. If there was no evidence of tumor growth during chemotherapy, whole-brain irradiation was started 4 weeks after the last cycle of chemotherapy (54 Gy in 30 fractions with 5 daily fractions of 1.8 Gy pr week) (10).

In the second study, a retrospective one, ('Irradiation-only group'), patients received postoperative whole-brain irradiation (50–54 Gy given in 25–30 fractions with 5 daily doses of 2 and 1.8 Gy respectively). Both patient groups were treated between 1983 and 1989.

The following pretreatment factors were investigated regarding possible prognostic values: age, clinical performance (ECOG scale), histology (grade 3 and grade 4), tumor localization, corticosteroid dependency after operation, extent of surgery (biopsy or resection), previous

history of fits (yes or no), length of history of fits, sex, ABO blood type, WBC count, and platelet count.

For the univariate survival analyses, the log-rank test was used to examine overall differences between survival curves (11). For the multivariate analysis Cox's proportional hazards regression model was used (12).

Results

The 'irradiation-only group' was established to get a comparison with the finding in the chemotherapy group. The distribution of patient characteristics in the two groups is shown in Table 1. The chemotherapy group contained a larger proportion of patients younger than 40 years and the patients had also a slightly better pretreatment performance status. A larger portion of the patients in the irradiation-only group had grade 4 tumors (91% compared to 71%). A greater proportion of patients had tumors located in the frontal lobes in the chemotherapy group. There were no significant differences between the groups concerning corticosteroid dependency, extent of surgery or sex.

The chemotherapy study suggested that the preirradiation chemotherapy led to a modest increase of the median survival and to a slightly increased proportion of long-term survivors. The most important finding was that a parallelism seemed to exist between chemotherapy sensitivity and radiation sensitivity (10).

Table 2 shows results of the univariate analysis of the 173 patients included in the two studies related to the most important prognostic factors. The median survival for the 35 patients with grade 3 tumors was 24 months compared to only 11 months for the 138 patients with grade 4 tumor ($p = 0.0001$). The 131 patients who were not steroid-dependent had a median survival of 14 months compared to only 6 months in the 42 patients who were corticosteroid dependent ($p < 0.0001$). The 146 patients with ECOG performance status 0–2 after craniotomy had a median survival of 14 months compared to only 4 months in the 27 patients with ECOG performance status 3–4 after craniotomy ($p < 0.0001$). More unexpected was the finding that patients with frontal lobe tumor had a significantly better survival than patients with tumor in other lobes. The Table also shows that age had a significant negative effect on survival. The patients with tumor resection had a median survival of 11 months compared to 16 months in biopsy-only patients, but this difference was not statistically significant.

No significant survival difference was seen between males and females.

We also performed univariate survival analysis on each of the two treatment groups (Table 3). Our findings suggest that combined chemotherapy and irradiation led to a better survival in grade 3 tumors. A median survival of 57 months for patients receiving combined treatment vs. 16 months for the irradiation-only group was observed. Among patients with frontal lobe tumors, those who received combined treatment had significantly longer survival than those who received irradiation alone. Only patients with ECOG 0–2 and patients not corticosteroid-dependent seemed to benefit from combined treatment. The table also suggests that females benefitted more from combined treatment than males. In patients younger than 40 years the median survival in the chemotherapy group was 18 months compared to only 11 months in the irradiation-only group. In older patients the median survival was 11 months in both groups.

A multivariate survival analysis of the two groups is presented in Table 4. Of the 12 variables examined, we

Table 1

Patient characteristics in the two treatment groups (n = 173)

Variables	Chemotherapy	Irradiation only	p-value
Age >40	58%	76%	0.01
ECOG 0–2	89%	78%	>0.05
Steroid dependency	25%	23%	NS
Biopsy only	13%	8%	NS
Frontal lobe location	58%	37%	<0.01
Grade 4	1%	91%	<0.001
Females	40%	42%	NS

Table 2

Univariate survival analyses of 173 patients with malignant gliomas

Prognostic factors	Median survival (months) (95% CI)		p-value
Age			
≥40	15	(11–20)	0.05
>40	11	(10–13)	
Histology			
Grade 3	24	(16–30)	0.0001
Grade 4	11	(10–12)	
Surgery			
Resection	11	(10–13)	NS
Biopsy	16	(6–34)	
Steroid dependency			
No	14	(11–15)	<0.0001
Yes	6	(4–10)	
Location			
Frontal lobe	16	(11–18)	
Other lobes	10	(9–12)	
Sex			
Males	11	(10–14)	NS
Females	13	(10–15)	
Treatment			
Chemotherapy	15	(10–20)	<0.005
Radiation only	11	(10–12)	
ECOG			
0–2	14	(11–15)	<0.0001
ECOG			
3–4	4	(3–6)	

Table 3

Univariate survival analysis of the two treatment groups stratified for other prognostic factors (n = 173)

Prognostic variables	Patients	Median survival (months)		p-value
		Chemotherapy group	Irradiation-only group	
Grade 3	35	57	16	<0.05
Grade 4	138	10	11	NS
Non-steroid dependent	131	20	11	<0.001
Steroid dependent	42	2	8	NS
ECOG 0–2	146	18	12	<0.001
ECOG 3–4	27	6	4	NS
Frontal lobe	84	20	12	<0.05
Other lobes	89	11	10	NS
Age ≤40	59	18	11	<0.05
Age >40	114	11	11	NS
Males	102	11	11	NS
Females	71	18	11	0.01

Table 4

Multivariate survival analysis of chemotherapy group and irradiation-only group (n = 173)

Variable	Relative death risk	95% CI	p-value
Grade 4	2.9	2.0–4.0	0.001
Steroid-dependent	1.9	1.4–2.5	<0.05
ECOG 3–4	1.8	1.4–2.5	0.05
Non-frontal lobe	1.7	1.4–2.1	0.01
Irradiation only	1.2	0.9–1.4	0.15

found 5 that independently were closely related to the prognosis. The most important one was histologic grade. Patients with grade 4 had 2.9 times higher relative death risk as compared to patients with grade 3 tumors. Patients who were corticosteroid-dependent after craniotomy had a 1.9 relative death risk as compared to patients who were off steroid medication after operation. Those who had a clinical performance status of ECOG 3–4 after craniotomy had 1.8 relative death risk compared to patients who had ECOG status 0–2. The multivariable survival analysis confirmed that patients with tumor locations in the frontal lobe had a better prognosis than patients with tumor locations in other lobes. Combining chemotherapy and irradiation may lead to a better survival than postoperative irradiation alone in malignant glioma, but the difference was not statistically significant ($p = 0.15$).

Discussion

The multivariate survival analysis identified 4 factors of independent significant prognostic value: histology, clinical performance status, corticosteroid dependency, and tumor location. Concerning the first two factors our findings are in general agreement with several previous studies. Postoperative corticosteroid dependency has not been reported previously as a factor of prognostic significance. In our study, the relative death risk was doubled if a patient had to continue steroid medication postoperatively. The question of prognostic importance of tumor location is debatable. Gehan & Walker (6) reported variations in survival depending on tumor location whereas other studies (8, 9) have reported no such correlations. In the present study, frontal location of the tumor was found to be positively related to survival. A possible explanation may be that frontal location leads to gross removal of the tumor bulk, thus relieving the intracranial pressure.

The patients with grade 3 tumors seemed to benefit most from combined chemotherapy and irradiation. There was probably no selection bias between the two treatment groups as all patients in the irradiation-only group had ECOG performance status of 0–2 and all had a gross total resection of the tumor.

By comparing the two treatment groups we found that chemotherapy followed by irradiation seemed to have had a positive impact on survival in patients who were off corticosteroid medication and had an initial good performance status. Also tumors located in the frontal lobe seemed to respond well to combined treatment. One explanation could be that tumors in this location have blood supply only from the internal carotid artery, whereas other tumor locations may in addition have a blood supply from the contralateral carotid and from the vertebral arteries.

We cannot explain the finding that women seemed to benefit more from intra-arterial chemotherapy than men.

By correlating sex with the major prognostic factors (ECOG status, corticosteroid dependency and histology) we found that these were randomly distributed between males and females.

Age was not found to be a predictor of survival in the multivariate analysis but in the univariate analysis younger patients did better than older. One explanation can be that the majority of patients with grade 3 tumors were younger than 40 years.

The relationship between the extent of neurosurgery and survival is conflicting. Chang et al. (13) found a strong relationship, whereas Brisman et al. (14) found no relationship. No correlation between the extent of surgery and survival could be found in the present study.

The relative death index table reported here (Table 4) may be used to identify distinct prognostic groups of patients and for discussions concerning treatment. It thus seems reasonable to adopt a more innovative regimen undergoing phase 2 studies for patients with a relatively high risk of death, whereas routine postoperative treatment could be given to patients with low relative death risk.

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