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Clinical Study

Prognostic significance of preoperative MRI scans in glioblastoma multiforme

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Abstract

Tumor necrosis, enhancement, and associated edema in patients with glioblastoma multiforme (GBM) represent biological variables that can be quantitated on preoperative MRI scans. We reviewed 48 highly selected patients, all of whom had supratentorial lesions, had undergone gross total tumor resection, and had received adjuvant treatments (radio- and chemotherapies). None of these patients had had surgery for recurrent tumor resection and none had harbored multifocal tumors. The median age was 50 years. The median Karnofsky performance score was 80. Multivariate analysis using the Cox regression model revealed that the strongest prognostic variable was the amount of tumor necrosis on preoperative scan ($P < 0.001$), with median survivals of 42, 24, 15, and 12 months for tumor necrosis grades of 0 (7 'pts'), I (11 'pts'), II (9 'pts'), and III (21 'pts'), respectively. The intensity of enhancement of the tumor nodule was another prognostic factor ($P = 0.003$), with median survivals of 35, 18, and 13.5 months for enhancement grades of 0 (2 'pts'), I (22 'pts'), and II (24 'pts'), respectively. The extent of peritumoral edema had a quadratic effect ($P = 0.001$), with grades I (19 'pts'), II (22 'pts'), and III (7 'pts') surviving for 24, 12, and 20 months respectively. Location and volume of tumors were not statistically significant predictors of survival ($P < 0.05$). In conclusion, in this highly selected group, GBM patients with little or no necrosis and with less tumor nodule enhancement on preoperative MRI survive longer than patients with greater amounts of necrosis and greater degrees of tumor enhancement. In addition, a moderate degree of peritumoral edema is associated with worse prognosis.

Introduction

Glioblastoma multiforme (GBM), the most malignant form of astrocytoma, remains a challenge to modern therapy. Despite advances in technology, including non-invasive techniques that provide accurate diagnoses and safe surgical procedures, the prognoses for these patients remain poor, with a median survival following diagnosis of approximately one year [1, 2]. The prognoses of patients with GBM, vary depending on several well-known variables including age [3], preoperative performance status [4], extent of tumor resection [5], location of tumor [6], neurological symptoms and duration [7], reoperation for recurrent tumor [8, 9], and whether or not X-ray therapy and/or chemotherapy have been given [2]. Moreover, even in a homogenous group of patients that receive the same mode of therapy, there is a difference in survival rates, with approximately 7.5%–12% of these patients surviving at least two years [10, 11] and 5% surviving up to 5 years [12]. This variation in prognosis and survival is most likely related to the biological behavior of these tumors and their interactions with

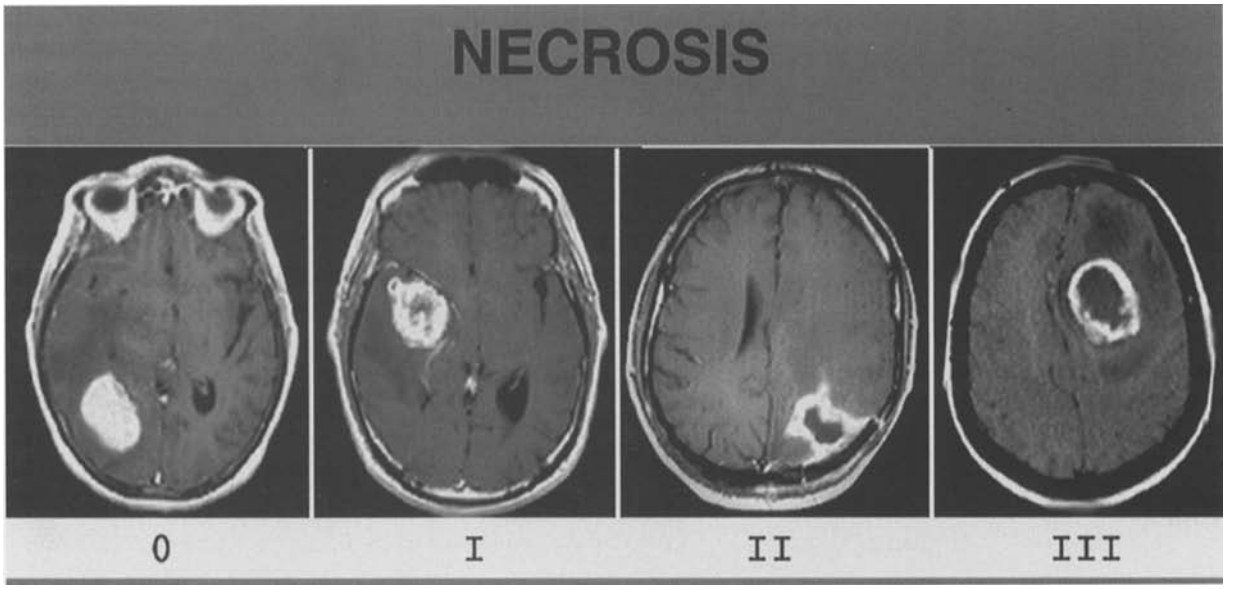

Fig. 1. Grades of necrosis. See text for details.

the host. Tumor enhancement, necrosis, and associated edema are radiological findings that represent biological variables. The purpose of the present study is to evaluate the prognostic significance of these variables as quantitated by preoperative magnetic resonance imaging (MRI) in patients with glioblastoma multiforme.

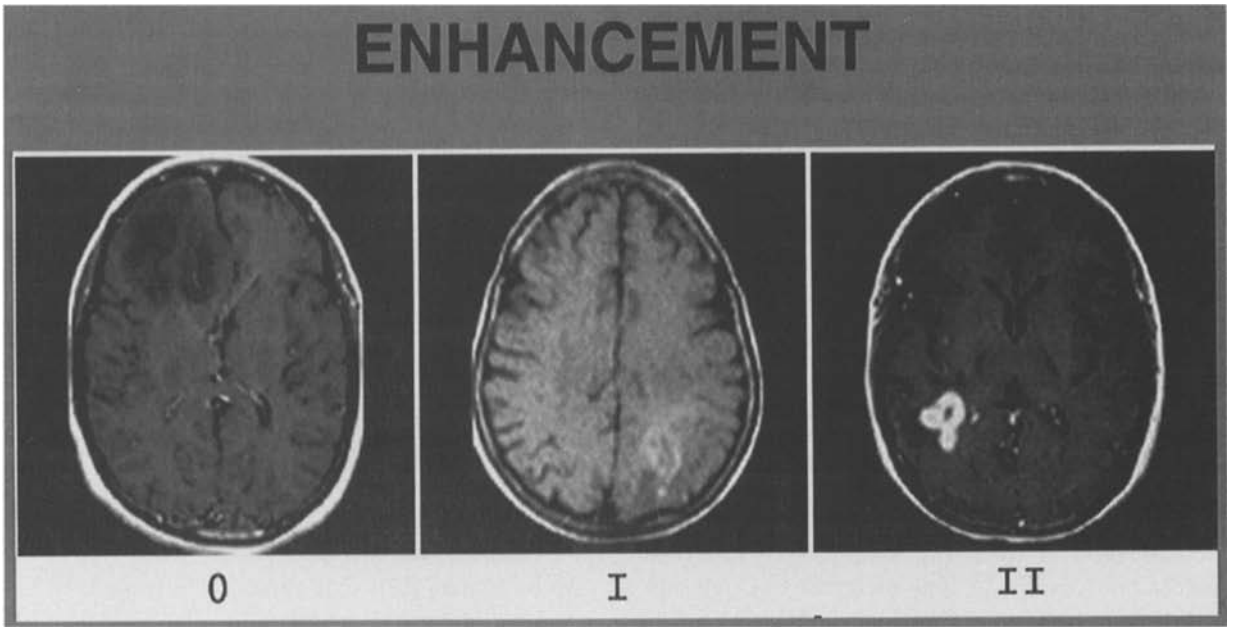

Fig. 2. Grades of enhancement (ENH). See text for details.

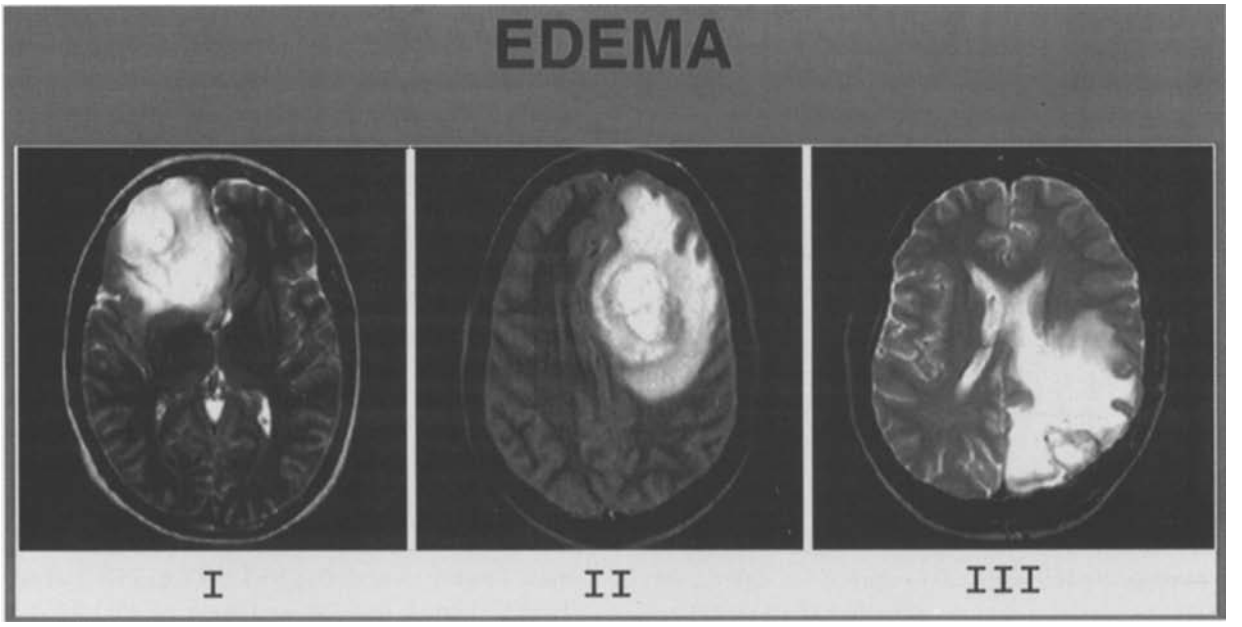

Fig. 3. Grades of edema. See text for details.

Patient selection

Preoperative MRI variables of 48 highly selected patients with the histological diagnosis of glioblastoma multiforme were reviewed [13]. Selection criteria were, (1) the patient had a preoperative and postoperative contrast MRI scan within 5 days of the operation in order to assess the extent of tumor resection [14], as well as a detailed neurological follow-up; (2) the patient harbored a supratentorial lesion that was not associated with tumor cyst at the time of surgery, and had no multifocal disease at the initial scanning; (3) the patient underwent gross total tumor resection as documented by the postoperative scan; (4) after operation, the patient received chemotherapy and either conventional or accelerated fractionated external beam radiation therapy up to a total tumor dose of 6000 cGY; and (5) the patient was receiving no glucocorticoids at the time of the initial scanning, as the diagnosis of brain tumor was normally made after the scans were obtained. We assume that the differences in the exact doses of contrast medium, the manners in which they were administered, and the types of MRI scanners used were randomly distributed among all patients studied and would not bias our results.

Definition of variables

The studied variables were age, sex, tumor location and volume, necrosis, enhancement, edema, neurological symptoms, preoperative Karnofsky score [15], type of radiotherapy, and duration of survival after operation. The tumor volume was measured according to the tested formula: volume = $\pi(a \cdot b \cdot c)/6$, where a, b, and c represent the three axes of the tumor in centimeters [16, 17]. Necrosis on MRI scans appears as an area of decreased T1 signal intensity that is often surrounded by a contrast-enhanced tumor nodule. The amount of necrosis, measured mainly from the post-contrast T1 images, was divided into 4 grades (Fig. 1): Grade 0 = no necrosis apparent on the MRI scan, Grade I = amount of necrosis is less than 25% of the tumor volume, Grade II = amount of necrosis is between 25% and 50% of the tumor volume, Grade III = amount of necrosis is greater than 50% of the tumor volume. Enhancement on MRI usually appears as an area of increased T1 signal intensity that surrounds a central area of necrosis. Enhancement of the tumor nodule measured on post-contrast T1 images was divided into three grades (Fig. 2): Grade 0 = no enhancement of the tumor nodule apparent on the

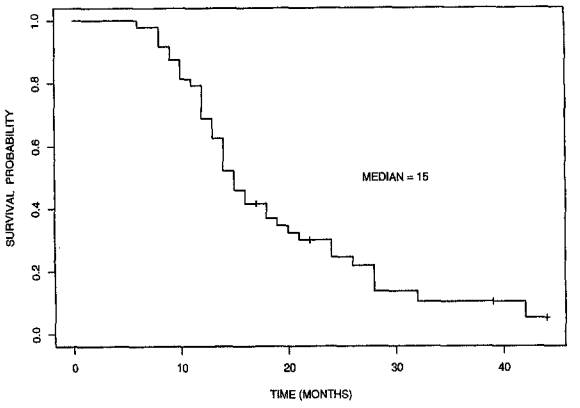

Fig. 4. Overall survival probability.

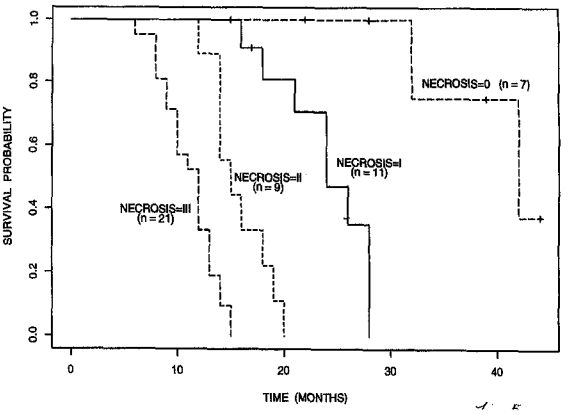

Fig. 5. Survival probability by tumor necrosis.

MRI, Grade I = signal intensity of the tumor nodule is less than that of fat, Grade II = signal intensity of the tumor nodule is equal to that of fat. Edema on MRI appears as a region of increased T2 signal intensity outside the gadolinium-enhanced area. Edema measured on T2 images was divided into 3 grades (Fig. 3); Grade I = amount of edema is less than the amount of tumor volume, Grade II = amount of edema is approximately equal to that of the tumor volume, Grade III = amount of edema is greater than that of the tumor volume.

Statistical methods

The Cox proportional hazards regression model [18] and the log rank test were used to assess the ability to predict survival for the variables: age, sex, Karnofsky performance status (KPS), neurological symptoms, tumor volume, type of x-ray therapy (*accelerated vs conventional*), grades of necrosis, enhancement and edema as measured by MRI, and binary indicators for tumor location in each of the temporal, occipital, parietal and frontal lobes, and left or right hemisphere. A final multivariate predictive model was obtained by performing a stepwise backward elimination. The Kaplan-Meier [19] method was used to generate survival plots.

Results

There were 26 females and 22 males. The age of patients ranged from 19 to 77 years with a median of 50 years. Twenty four (50%) patients had a KPS of 80, 21 (44%) had a KPS of 90, and the remaining 3 (6%) had a KPS ≤ 70. Twenty nine (60%) patients had a lesion in the right hemisphere, 19 (40%) in the left hemisphere, and 17 (35%) patients had a tumor encroaching on an adjacent lobe. Twenty four (50%) patients received accelerated fractionated radiation and 24 (50%) received conventional radiotherapy. Overall, 41 of 48 (85%) patients have died. The median survival was 15 months, with 95% confidence interval (14–20) months (Fig. 4). The variables individually predictive of survival are shown in Table 1. The variables predictive of survival after multivariate analysis using the Cox model are shown in Table 2. The amount of tumor necrosis indicated on preoperative scan was the strongest

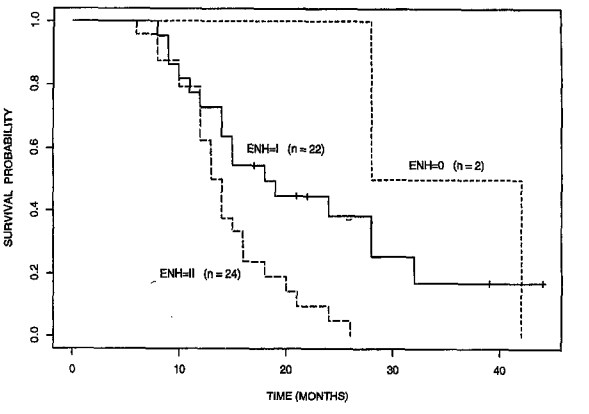

Fig. 6. Survival probability by tumor enhancement.

Table 1. Covariates individually predictive of survival time

Variable	Favorable	P-value
Edema	Low or High	< 0.001
Necrosis	Low	< 0.001
Enhancement	Low	0.003
Age	Younger	0.030
X-ray	[a] AF	0.063
Headache	Not Present	0.075

[a] AF = Accelerated fractionation.

prognostic factor (P < 0.001), with median survivals of 42, 24, 15, and 12 months for patients with tumor necrosis grades of 0 (7 'pts'), I (11 'pts'), II (9 'pts'), and III (21 'pts'), respectively (Fig. 5). Comparisons of necrosis subgroups 0, I to II, and II to III yielded respective two-sample log rank p-values of 0.001, 0.0009, and 0.0004. The intensity of enhancement of tumor nodule was another prognostic factor (p = 0.003), with median survivals of 35, 18, and 13.5 months for enhancement grades of 0 (2 'pts'), I (22 'pts'), and II (24 'pts'), respectively (Fig. 6). Comparisons of enhancement subgroups I to II yielded a p-value of 0.006. The extent of peritumoral edema had a quadratic effect (p = 0.001), with grades I (19 'pts'), II (22 'pts'), and III (7 'pts') surviving for 24, 12, and 20 months respectively (Fig. 7). Comparisons of edema subgroups I to II and II to III yielded respective log rank p-values of 0.005 and < 0.001. In addition, younger patients survived longer than older ones (Table 1). However, multivariate analysis lowered the significance of age on survival (Table 2). Sex, neurological symptoms, type of x-ray therapy, location, and volume of tumor on preoperative scans were not statistically significant predictors of survival in this series. Due to the small overall sample size (n = 48), all of the results reported here are

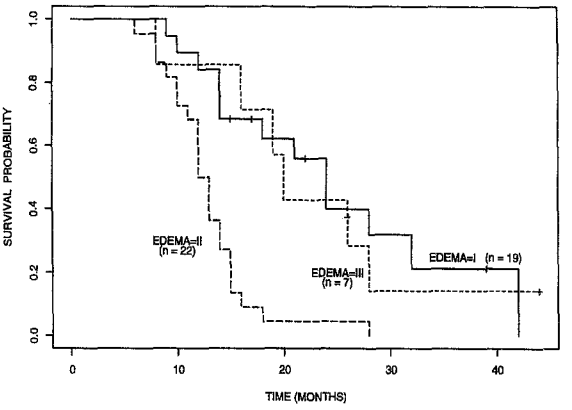

Fig. 7. Survival probability by tumor edema.

at most suggestive of general patterns in the larger population of glioblastoma patients, and further studies are needed to confirm them.

Discussion

There are several variables that affect prognosis and survival of glioblastoma multiforme patients: 1) younger patients survive longer than older patients [3]; 2) patients with good performance status (KPS ≥ 70) survive longer than patients with poor performance status (KPS ≤ 70) [4]; 3) patients who undergo gross total tumor resection and reoperation for recurrent disease survive longer than patients who undergo less tumor resection [5, 8, 9]; 4) epilepsy as a first symptom and frontal location of these tumors are believed by some to carry a positive effect on survival [7, 20]; and 5) patients who receive radiation therapy and chemotherapy after excision of these tumors have better survival rates than those who do not [2, 11]. These are well-known documented variables. However, the question re-

Table 2. Multivariate cox model for predicting survival[a]

Variable	Coefficient estimate	Standard Error	P-value	
Necrosis	3.54	0.576	< 0.001	
Edema	− 6.15	2.130	0.004	0.001
Edema^{2}[b]	1.30	0.525	0.014	
Enhancement	1.15	0.382	0.003	

[a] Likelihood ratio = 92.3 on 4 degrees of freedom (p = 0), 41 deaths out of 48 patients.
[b] Edema^2 = Edema squared.

mains, 'Why do certain patients with the histological diagnosis of glioblastoma survive longer than other patients even though they receive the same mode of treatment and are comparable with respect to other known variables?'. There is no doubt that the answer to this question is related to the various biological factors that are intrinsic to each glioblastoma tumor and that vary from one host to another. With the advance in technology and the advent of MRI scans, we are able now to identify, assess, and quantitate some of the morphological findings that represent tissue changes [21] and are related to the biological behavior of these tumors. Our study shows that necrosis, enhancement and edema are additional prognostic variables of survival in this selected group of GBM patients.

Necrosis

Tumor necrosis is a common feature of malignant neoplasms. In regard to gliomas, the extent of necrosis has become increasingly important in the histological grading of these tumors because of its correlation with a less favorable prognosis [13, 22]. The appearance of tumor necrosis either on diagnostic images or on pathological studies indicates a more malignant phenotype of brain tumors. Low-grade gliomas usually do not show any necrosis on preoperative scans. However, highly malignant cerebral tumors generally are associated with a significant amount of necrosis [23]. Although detection of necrosis on MRI scan should be a necessary criterium for including glioblastoma in the differential diagnosis, not all histologically diagnosed glioblastomas exhibit such findings. We had 6 (13%) glioblastoma patients who showed no evidence of necrosis on the MRI. Our series showed that this variable, *i.e.* amount of necrosis on MRI scan, is a very important radiological finding in predicting survival in this group of GBM patients. Patients with no or small amounts of necrosis on preoperative scans survived longer than patients with greater amounts of necrosis ($P < 0.001$). To our knowledge, there is no study correlating the amount of necrosis as measured on preoperative scans in GBM patients with prognosis and survival.

Enhancement

Enhancement by paramagnetic contrast agents requires active disruption of the BBB in order to allow large molecules like gadolinium DTPA to accumulate within the tumor nodule [24, 25]. The primary effect of the paramagnetic contrast agent is shortening of T1 relaxation time. Enhancement on MRI usually appears as an area of increased T1 signal intensity that surrounds a central area of necrosis. In patients with GBM, the histopathological correlation of this finding on MRI is related to solid tumor tissue with pathologic neovascularization and endothelial proliferation [26]. Moreover, electron microscopic studies of gliomas have revealed a direct relationship between the degree of abnormality in capillary endothelial cells and their tight junctions and the degree of anaplasia [27, 28]. In low-grade gliomas, new capillary formations resemble normal cerebral capillaries with maintenance of the BBB, and, therefore, no enhancement is seen [29]. On the other hand, angiogenesis in more malignant tumors leads to the formation of abnormal blood vessels, with absent or incomplete BBB, which allows enhancement by the contrast agent [28–30]. Although GBM belongs to the latter group of tumors, some glioblastomas may exhibit minimal or no gadolinium enhancement whatsoever [23]. Our data showed that glioblastoma patients with no or minimal enhancement on post-contrast MRI scans survive longer than those with significant enhancement ($P = 0.003$). Unfortunately, reports show that only 4% of GBM patients show no enhancement on post-contrast scans [31], and our findings are consistent with this figure. The poor prognosis that was associated with the greater degree of enhancement in our series could be related to more angiogenesis. However, further studies are needed to determine the relationship between angiogenesis and enhancement as seen on brain scans, as well as survival in malignant brain tumors.

Edema

Peritumoral edema may be secondary to alteration of the normal BBB, resulting in abnormal leakage of

water and plasma proteins with a preferential accumulation in the larger extracellular spaces of white matter with respect to those of gray matter. This increased water content in abnormal tissue requires only minimal BBB breakdown [21] and results in increased T2 relaxation time [32, 33]. A large amount of edema around a glioma might suggest a more malignant phenotype [23]. Levin *et al.* [34], in a study of 61 patients, found that the presence on a CT scan of a large peritumoral low-density area (edema) was a favorable prognostic sign relative to the time of tumor progression. They suggested that this unexpected finding might possibly be related to vasogenic edema and breakdown of BBB, allowing the passage of immune reactive cells or proteins.

It is very likely that specific factors produced by the tumor are responsible for the brain edema [35]. Sawaya *et al.* [36] demonstrated a significant and inverse correlation between tPA and the presence and degree of peritumoral brain edema as measured on preoperative scans in a glioblastoma group. The implication of these findings is that proteolytic enzymes might, at least in part, contribute to the formation of peritumoral brain edema. Our study showed that both severe edema and minimal edema were favorable prognostic signs of survival. This result could have been biased by the fact that in some cases infiltrating tumors were counted as edema due to the difficulty of separation between tumor and surrounding edema [26, 37].

Volume and location

Wood *et al.* [38], and Reeves and Marks [39] found no relationship between the size of the tumor, as estimated from cross-sectional areas on preoperative CT scans, and survival of patients with GBM. Onoyama *et al.* [40] found increased survival for patients with right hemispheric tumors as compared to left hemispheric tumors. Gehan *et al.* [6] found that parietal tumors carried a worse prognosis, and Pigott [20] found that frontal tumors had a significant positive effect on survival. On the other hand, comparisons of survival for tumors in the frontal, temporal, parietal, and occipital lobes have generally not revealed significant differences [41]. Our data showed that location and preoperative volume of the tumor are not significant predictors of survival.

Conclusion

The survival of this highly selective group of patients with the histological diagnosis of GBM can be predicted from preoperative MRI scans. Patients with little or no necrosis and with less tumor enhancement survive longer than patients with a greater amount of necrosis and a greater degree of tumor enhancement. In addition, a moderate degree of peritumoral edema is associated with worse prognosis. To our knowledge, this is the first study that correlates these biological variables as they appear on preoperative MRI scans with the outcome of therapy. Future studies of treatment results for GBM should include these additional prognostic variables. In addition, it will be interesting to identify and correlate the specific molecular factors that are responsible for these biological variables with survival.

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