LIOBLASTOMA multiforme is the most common malignant cerebral tumor in adults. Its prognosis is poor: the median survival rate is approximately 1 year, despite treatment with a combination of surgery, radiotherapy, and chemotherapy.\(^2,3,18,21\) After a recurrence at the initial location, a combination of surgery and chemotherapy remains the standard treatment.\(^1,16\)

To determine the patient’s prognosis, different factors have been analyzed in previous studies, such as age, KPS score, localization and size of the tumor, extent of the surgical resection, histological findings, and use of radiotherapy and/or chemotherapy.\(^13,17\) The size of the tumor was usually assessed by measurement of the diameters or estimation of the volume, but these features were found to be not significantly correlated with survival.\(^22\)

We took advantage of a gene therapy trial in progress at our institution and used the thymidine kinase/ganciclovir regimen to treat recurrent GBM. In the process, we developed a new criterion for adjusting the dose of therapeutic cells injected into the walls of the surgical cavity. Instead of considering the tumor mass as an indication to determine dosages, we took into account the real surface to be injected, which was the interface dividing normal from tumor tissue. The extent of this interface, which we called the STV, and therefore the dose of delivered cells, was assessed using preoperative MR images (Fig. 1).

The aims of this study were 1) to assess the clinical value of measuring the STV with respect to prognosis; 2) to analyze its fluctuations in responding and nonresponding patients; and 3) to test the relationship between STV and the usual clinical features.

Clinical Material and Methods

Patient Population

Sixteen patients who presented with recurrent GBM between 1995 and 1998 were enrolled in a gene therapy trial. All patients had previously been treated with a combination of surgery, conventional radiotherapy, and often chemotherapy. Their mean age was 51 years (range 40–62 years), the sex ratio was 10:6 (male/female), their mean KPS score was 80, and the mean interval between the first

Abbreviations used in this paper: GBM = glioblastoma multiforme; KPS = Karnofsky Performance Scale; MR = magnetic resonance; STV = surface of tumor volume; TV = tumor volume.
treatment and recurrence was 10 months (range 5–17 months). All patients presented with a GBM according to the World Health Organization–Saint Anne criteria, as assessed by two independent neuropathologists. In each case informed consent was obtained before treatment was initiated.

A gross-total resection was performed when possible by using a routine neurosurgical procedure. Subtotal or total resection was achieved in all cases, as assessed on postoperative MR images. The resection was followed by injection of transfer cells into the walls of the surgical cavity. The number of cells was proportional to STV, in accordance with the published protocol. The mean number of injected cells was $281 \times 10^6$ (range $70–530$). We decided not to use a single concentration of cells because of the risk of intracranial hypertension with high-volume injections. Thus, the concentration used for large numbers of cells was higher than for smaller numbers of cells. Hence, the injected volume varied from 6 ml (for doses $\leq 450 \times 10^6$ cells) to 12 ml (for doses $> 450 \times 10^6$ cells).

Patients who displayed a stabilization or regression of postoperative contrast enhancement on 4-months follow-up MR images were defined as responding and the others as nonresponding. The results of this trial have shown a large range of responses among patients.

Neuroradiological Methods

The MR studies were performed using a 1.5-tesla unit (Sigma; General Electric Medical Systems, Milwaukee, WI). Preoperative MR imaging consisted of an enhanced sagittal $T_1$-weighted sequence, axial $T_2$-weighted sequences, and axial spoiled three-dimensional gradient-echo image acquisition obtained after intravenous administration of 0.2 mmol/kg gadolinium-diethylenetriamine pentaacetic acid (Dotarem, Guerbet, France).

Preoperative postcontrast images were analyzed on a separate workstation (Advantage Windows, Spark 20; General Electric) by using commercially available software (General Electric, Buc, France). The measurements were performed using electronic calipers with a manual trace on each 3-mm-thick section from serial axial images. The observer measured the area and total length of the enhanced area surrounding the lesion. The total length consisted of the interface between the tumor and normal brain tissue, and did not represent the entire tumor surface (Fig. 1).

The TV and the STV were determined according to the following formulas: $TV \ (cm^3) = \sum (area \ [mm^2] \times 3 \ mm \ [section \ thickness])/1000$; $STV \ (cm^2) = \sum (total \ length \ [mm] \times 3 \ mm \ [section \ thickness])/100$.

Statistical Analysis

The nonparametric Spearman test was used to compute the correlation between tumor size parameters and survival. The nonparametric Mann–Whitney test was used to analyze the differences between groups. A probability value of less than 0.05 was considered significant.

Analysis was performed using commercially available software (StatView; SAS Institute, Inc., Cary, NC).

Results

Overall Survival

No significant correlation has been found between survival and the clinical features usually investigated, for example: age of the patient ($p = 0.75$), KPS score ($p = 0.8$), and disease-free interval ($p = 0.48$). No significant correlation has been observed between survival and existence of residual tumor ($p = 0.49$).

The mean STV was 29.2 cm$^2$ (range 8–55 cm$^2$); the mean TV was 23.8 cm$^3$ (range 3–55 cm$^3$). The correlation between STV and TV was high ($r = 0.948$) and significant ($p < 0.001$). No significant correlation was found between STV and other clinical features.

The TV was not significantly correlated with survival (Spearman test: $r = -0.39$, $p = 0.15$), whereas the STV was (Spearman test: $r = -0.54$, $p = 0.03$; Fig. 2a).

![Fig. 1. Preoperative MR images used to determine the extent of tumor–brain interface in a left temporal recurrent GBM. Left: White line marks the contrast-enhancement perimeter on each 3-mm section, defining the TV. 1 = heterogeneous contrast enhancement; 2 = normal tissue; 3 = the temporal horn; 4 = the old surgical cavity; 5 = the tentorium incisure. Right: White line delimits the perimeter of the interface between tumorous and normal tissue on each 3-mm section, defining the STV.](image-url)
Separate Analysis of Responding and Nonresponding Patients

Based on predefined criteria, four patients responded to treatment and 12 did not respond.12 There was no significant relationship between STV or TV and existence of a response (p = 0.08). The median duration of survival was 546 days for responding and 175 days for nonresponding patients. Because the difference between the two groups was statistically significant in a comparative analysis (U-test: p = 0.04), we performed a separate analysis of these two populations.

Nonresponding Patients. The STV was negatively correlated with survival in nonresponding patients (Spearman test: r = −0.6, p = 0.04), whereas the TV was not (Spearman test: r = −0.6, p = 0.06; Fig. 2b).

Responding Patients. There was a trend toward a positive relationship between the STV and survival (Spearman test: r = 0.6, p = 0.29), but it is not possible to determine this conclusively because of a lack of statistical power (Fig. 2c).

Discussion

Until now, some variables, such as age, KPS score, and histological findings, have been associated with the prognosis of GBM. However, although in some studies a correlation has been shown between survival and the amount of residual tumor, no feature related to the initial tumor size has been found to correlate with survival and therefore to be useful for prognostic purposes.22

This is in contrast with the usual findings in oncological studies, in which, in a majority of cases, the size of the tumor is one of the features commonly used to predict evolution of the disease.10

Our data indicate no correlation between tumor size and patient survival, when assessed by lesion volume. However, surprisingly, when defined by the STV, improvement of survival becomes significantly correlated with small tumors. In fact, in the case of a spherical model of tumor, which is rarely seen in malignant gliomas, there is a theoretical relationship between STV and TV, because TV/STV is proportional to the radius. However, when the shape of the tumor is more complex, STV augments more rapidly than TV. Thus, although it needs to be confirmed in a larger group of patients, this discrepancy presumably reflects the complexity of tumor shape. The difference observed between TV and STV with respect to survival indicates that taking into account the interface between normal and pathological tissue may better enable the physician to assess tumor aggressiveness than the size of the lesion itself. It may reveal the probability of finding tumor cells inside surrounding normal cerebral tissue. These cells are known to constitute the basis for most relapses, given that 95% of GBMs recur in the immediate vicinity of their initial location.13 In agreement with these observations, in all patients in this clinical trial the relapses occurred inside or near the surgical cavity.12 In fact, these cells probably represent the aggressive portion of the tumor in terms of biological activity. Their malignant behavior can be related to a higher mitotic activity, but also to an increased ability to migrate from the tumor to the normal brain. In fact, the designation of the Ki labeling index as a predictor of survival time for patients with malignant gliomas remains controversial. Moreover, proliferation and migration of these cells may have an inversely proportional relationship, as shown in recent studies.14

These isolated cells are the most difficult part of the tumor to remove because of its close relationship with healthy brain and its normal macroscopic appearance.2 Thus, the surface of contact between the lesion and normal tissue could represent the ideal area to treat for control of the disease.

A separate analysis of responding and nonresponding patients has shown interesting differences. Among nonresponding patients, the size of the tumor is inversely proportional to survival, which indicates that for these patients, small tumors have a better prognosis. As in the whole patient population, this may be due to reduced dissemination and/or to better efficacy of the treatment. It could explain why, with in situ approaches, better results are observed in small tumors than in large ones.5 Thus, ra-
diosurgery and brachytherapy are associated with better clinical results in tumors less than 3 cm in diameter.19,20 On the other hand, among responding patients, the more the surface grows, the better the prognosis. This can only be called a trend because the number of responding patients is too small to justify a conclusion, and one of them died accidentally from a cranial trauma 1 month after the response and therefore could not be assessed for survival. The dose of injected cells is proportional to the STV, as assessed before treatment. Because the concentration of injected cells in the walls of the surgical cavity increases with the total dose of injected cells, it probably increases the ratio of transfer cells to tumor cells.15 The same number of transfer cells can be delivered to the brain in a lower volume, and can therefore limit effusion of cells and leakage at the surface. Thus, this result could indicate an effect of the concentration of injected cells on efficacy. A larger group of patients is required to confirm this tendency.

Improvement of the homogeneity of three-dimensional distribution of these cells when injected in a wide area may be involved too, because the injection procedure is actually performed manually and remains a challenge for the surgeon in terms of reproducibility. Finally, it could be argued that in larger tumors the number of in-cycle tumor cells at the periphery of the lesion increases and therefore, a bystander effect might become more likely.7,9,23

Conclusions

These observations indicate that STV is a promising tool for predicting the evolution of malignant gliomas. To evaluate more accurately the clinical value of this procedure, a large study, including a greater number of patients, is required.

However, future gene therapy trials in which an in situ strategy is used should take into consideration the concentration and diffusion of transfer cells and/or vectors as an important issue for efficacy.9,15

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References


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