Cystic glioblastoma multiforme: survival outcomes in 22 cases

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Object. The goal of this study was to determine whether the presence of a large tumor cyst was associated with improved outcome in patients undergoing surgery for newly diagnosed glioblastomas multiforme (GBMs) by comparing these patients with a matched cohort of patients with noncystic GBMs in clinical features, tumor imaging characteristics, survival, and time to tumor recurrence after surgery.

Methods. A retrospective analysis was conducted in 22 patients by using imaging information and chart reviews of operative reports of GBMs with large cysts (≥50% of tumor volume) at The University of Texas M. D. Anderson Cancer Center between 1993 and 2002. Clinical and neurosurgical outcomes and recurrence rates were studied. A statistical comparison was made with a matching cohort of 22 patients with noncystic GBMs.

No significant differences in clinical variables were found between the cohort with cystic GBMs and the matched cohort with noncystic GBMs. To avoid bias in preoperative assessment of tumor volume, the tumor burden was compared in patients whose tumors had cysts (excluding the cystic mass) and in patients whose tumors did not contain cysts. There was no statistically significant difference between the two groups (p = 0.8). In patients with cystic GBMs the median survival time after surgery was 18.2 months (95% confidence interval [CI] 11.9–24.5 months) and at 2 years 43% of the patients were still alive. In comparison, in patients with noncystic GBMs, the median survival time was 14.3 months (95% CI 12.1–16.4 months) and only 16% of patients were alive at 2 years. The median time to tumor recurrence was 7.6 months (95% CI 0.01–18 months) in patients harboring cystic GBMs and 4.2 months (95% CI 1.8–6.6 months) in the matched cohort (log-rank test, p = 0.04). In the cystic GBM group, no recurrence was observed in 53% of patients at 6 months, 45% at 1 year, and 38% at 2 years after surgery, whereas the corresponding numbers for the noncystic group were 36, 14, and 9%, respectively.

Conclusions. The results indicate that patients harboring a GBM that contains a large cyst survive longer and have a longer time to recurrence than those who lack such a cyst. This is the first such observation in the literature.

KEY WORDS • glioblastoma multiforme • prognostic factors • tumor recurrence • cystic brain tumors • tumor invasion

Glioblastoma multiforme is the most malignant form of astrocytoma. Despite advances in surgery, adjuvant chemotherapy, and radiotherapy, in general GBMs remain associated with a poor prognosis and with fairly rapid, fatal progression. The median duration of survival is approximately 50 weeks and a small select group of patients (7.5–12%) survive for at least 2 years. Several variables affect the prognosis with GBM, including patient age, preoperative KPS score,16 tumor location, extent of tumor resection, the preoperative MR imaging characteristics of the tumor (such as the grade of necrosis and contrast enhancement), and whether patients have received additional treatment, including radiation therapy and adjuvant chemotherapy.12,13,16,19,21,31,32,35,38,39,42,44 Although the presence of a cyst in low-grade gliomas has been shown to be associated with an improved outcome,9,17,25–27,34,43 in no series to date has the outcome of patients with GBMs been evaluated with respect to the presence or absence of a cyst. A review of previous reports of long-term survivors with GBM revealed no comments about the presence of a cyst in the tumor as a significant prognostic variable.5,6,29,31,33,40,41,46,47 Consequently, the purpose of this study was to determine the prognostic implication of a cyst in patients with GBMs. To address this issue we compared the outcomes (that is, survival and tumor recurrence) of 22 patients with cystic GBMs with outcomes of a matched cohort of patients with noncystic GBMs.

Clinical Material and Methods

Patient Population

In a search of the neurosurgical database at The University of Texas M. D. Anderson Cancer Center, we identified 322 patients with newly diagnosed GBMs who were treated between June 1, 1993, and February 28, 2002. Twenty-two of these patients harbored a large cyst, the existence of which was verified by both neuroimaging and surgery. In all cases, the cysts constituted more than 50% of the tumor volume, based on preoperative MR imaging studies (Fig.
and the operative report documented the unequivocal finding of a cyst. A review of patients’ charts was conducted to obtain information on their ages, sexes, KPS scores, and clinical presentations. All cases were reviewed a second time to confirm the histological diagnosis of GBM according to the World Health Organization classification. Data were obtained regarding the time to recurrence or growth of the residual tumor, and each patient’s vital status at the time of the analysis was determined on the basis of the M. D. Anderson tumor registry. For this study, the requirement to obtain informed consent from patients was waived by the M. D. Anderson Institutional Review Board.

The preoperative MR images that had been obtained in all patients were reviewed. For each tumor, the extent of contrast enhancement, the functional grade (proximity to eloquent cortex), and the mass effect on the surrounding brain were measured. Postoperative MR imaging, obtained in all patients within 48 hours after tumor resection, was prospectively analyzed for the purpose of determining the extent of resection that had been achieved.

Tumor volume was defined as the area of enhancement in contrast-enhanced T1-weighted MR images and was calculated using the Vitrea 2 program. The volume of the enhancing rim in cystic GBMs (Fig. 1) was calculated using the “perimeter” method, wherein each data value that falls within the defined region and within the predefined thresholds for the three volume measurements (combined, cystic portion, and enhancing) is evaluated by the program. The program automatically “draws” color-coded contours around the regions for the enhancing and nonenhancing volumes and highlights the volume of solid parts and borders between the outer and inner cyst contours. For each patient with a cystic GBM, the volume of the cyst was determined, and the tumor burden (excluding the cystic mass) in these patients was compared with the tumor burden in patients without cystic GBMs.

Follow-up MR images were obtained at 1 month after surgery and every 3 months thereafter to identify recurrence or residual tumor growth. After undergoing cytoreduction surgery, the patients received radiotherapy and adjuvant chemotherapy.

Statistical Methods

Each of the 22 patients with a cystic GBM was matched to a patient with a noncystic GBM. Table 1 summarizes the characteristics used to match these two groups. The control group was chosen from a group of previously untreated patients with GBMs. These patients underwent craniotomy for resection within a maximum of 1 year from the surgical date of the cystic GBM group, had a tumor with no cystic component, had ages within 5 years of those in the cystic GBM group, and had a KPS score that was within 10 points of the patients in the other group. The extent of resection of tumors in the noncystic GBM group was matched to include a resection volume within 5% of that of tumors in the cystic GBM group. For each case more than one potential match was found, and the closest was picked. The McNemar exact test and the Wilcoxon signed-rank test were used...
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Table 1: Matching characteristics of patients harboring cystic GBMs and those harboring noncystic GBMs

<table>
<thead>
<tr>
<th>Matching Characteristic</th>
<th>Matching Criterion</th>
<th>No. of Patients W/ Successful Match*</th>
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<tbody>
<tr>
<td>date of surgery</td>
<td>w/in 1 yr of surgery</td>
<td>21 of 22</td>
</tr>
<tr>
<td>patient age</td>
<td>w/in 5 yrs of age</td>
<td>22 of 22</td>
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<tr>
<td>preop KPS score</td>
<td>w/in 10 points</td>
<td>21 of 22</td>
</tr>
<tr>
<td>GBM status</td>
<td>newly diagnosed, previously untreated lesion</td>
<td>22 of 22</td>
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<tr>
<td>initial treatment</td>
<td>craniotomy for resection</td>
<td>22 of 22</td>
</tr>
<tr>
<td>extent of tumor resection</td>
<td>w/in 5% of tumor vol</td>
<td>20 of 22</td>
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</tbody>
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* Overall, 19 patients were matched successfully on all criteria, two patients were matched on five of the six criteria, and one patient was matched on four of the six criteria. Repeating the analysis after excluding the last three patients and their matches resulted in similar trends.

Results

Clinical and Imaging Characteristics

Table 2 provides the frequency distribution of clinical and neuroimaging characteristics for the cases of cystic GBM and the matching noncystic GBM controls. There were no differences between the clinical or neuroimaging features of these two groups. The cystic GBM group consisted of 12 men and 10 women. The noncystic GBM group included 13 men and nine women. In both groups, the KPS scores ranged from 50 to 100 (median 90). In four patients (18%) in the cystic GBM group and in five patients (23%) in the matching group seizures were a clinical manifestation of the disease. The lesion involved eloquent areas of the brain (Grade III) or near-eloquent areas (Grade II) in 96% of cases in the cystic GBM group and in 91% of cases in the noncystic GBM group. Both groups presented with a similar degree of preoperative tumor mass effect and contrast enhancement on MR images (Grade 2 or 3 enhancement in at least 95% of each cohort). There was no significant difference between the two cohorts with respect to the amount of edema surrounding the tumor, although the noncystic GBM group had a somewhat higher proportion of Grade 3 edema, which may partially account for the similarity in mass effect noted earlier, despite the larger total volume in cystic GBMs. In addition, there was no statistically significant difference in tumor burden (p = 0.8) between the group with cystic tumors (median 38.6 cm³, range 6.5–15.8 cm³) and the group with noncystic lesions (median 41.26 cm³, range 3.54–215.03 cm³). Three patients in the cystic GBM group and two patients in the noncystic GBM group had preoperative hemorrhage.

Surgical Outcomes

Patient outcomes are shown in Table 3. With regard to their neurological performance status following resection, the cystic and noncystic GBM cohorts had similar median KPS scores (90 and 85, respectively). Only two patients in the cystic GBM group had neurological complications (9%), compared with three patients (14%) in the noncystic...
GBM group. The patients in both cohorts experienced a median hospital stay of 3 or 4 days.

Length of Survival

Patients with cystic GBMs had a median actuarial length of survival from the time of diagnosis of 18.7 months (95% CI 4.0–33.4 months) and 45% of patients were alive at 2 years (Fig. 2). Their median actuarial survival from the time of surgery was 18.2 months (95% CI 11.9–24.5 months) and 43% of patients were alive at 2 years (Table 3). In the noncystic GBM group, the median length of survival after diagnosis was 14.4 months (95% CI 11.7–17 months), and only 15% of patients survived for 2 years (log-rank test, \( p = 0.1 \)) (Fig. 2). The median duration of survival from the time of surgery was 14.3 months (95% CI 12.1–16.4 months), and 16% of patients were alive after 2 years (log-rank test, \( p = 0.12 \)) (Table 3).

Time to Recurrence or Regrowth of the Tumor

The median actuarial time to recurrence or regrowth of the tumor after surgery was 7.6 months (95% CI 0–18 months) in the cystic GBM group and 4.2 months (95% CI 1.8–6.6 months) in the matched control group (Table 3 and Fig. 3). In the cystic GBM group no tumor recurrence or regrowth was observed in 53% of patients at 6 months, in 45% at 1 year, and in 38% at 2 years after surgery; the corresponding numbers for the noncystic GBM group were 36, 14, and 9%, respectively. As shown in Fig. 3, there was a statistically significant difference in the progression-free survival curves between the cystic and noncystic GBM groups (log-rank test, \( p = 0.04 \)).

Histological Analysis

In all 22 cases, a review of the pathological slides revealed GBM. In two cases, specimens were obtained in which the relationships among the lumen, tumor wall, and surrounding brain parenchyma could be analyzed. In both these cases there was a narrow rim of tumor around the cyst lumen. Limited infiltration of surrounding brain parenchyma was found in this pericystic tumor (Fig. 4). In contrast, noncystic GBMs displayed the more extensive infiltration typical of other GBMs.

Tissue sections of cystic and noncystic GBM surgical specimens were reviewed, with specific attention given to the identification of morphological features associated with recognized GBM subtypes (giant cell, small cell, and epithelioid) or any features that might suggest an oligodendrogial component or oligodendroglial differentiation. We found that in all patients the tumors exhibited the charac-

![Graph showing Kaplan–Meier estimates of overall survival in patients with cystic GBMs and those with noncystic GBMs. The differences between the two groups’ curves are not significant (\( p = 0.1 \)).](image-url)
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teristic features of a classic GBM, including nuclear and cellular pleomorphism, prominent numbers of mitoses, microvascular proliferation, and necrosis. No case of giant cell GBM or other GBM variants was identified. No features suggestive of oligodendrogial differentiation were seen in any patient. Because all tumors exhibited prominent mitotic activity and the results of previous studies indicate that MIB-1 antigen detection is not helpful in subtyping GBMs, MIB-1 immunostaining was not performed. In summary, there were no identifiable specific or unique morphological features associated with either cystic or noncystic GBM tumors and no discernable differences in mitotic activity.

Discussion

A cyst is commonly found in low-grade astrocytomas (>50% of cases) and in most pilocytic astrocytomas. In these low-grade tumors, cysts have been correlated with a better prognosis.17,23,25,36 Cysts can also be found in higher grade lesions, but the presence of a cyst in GBMs has not been previously evaluated with respect to patient outcomes. Although other predictors of long-term survival in patients with GBMs have been described (including aggressive tumor removal, multimodal therapy, younger patient age, high KPS scores, tumors overexpressing p53 or mdm2, and lower tumor proliferation rates),5,6,20,27,30,41,46,47 to our knowledge, this is the first study that focuses specifically on the outcome of patients who undergo surgery for newly diagnosed GBMs with a large cystic component.

We analyzed the neuroimaging and surgical reports of 22 patients who harbored GBMs with a large cystic component and compared them with similar reports from a noncystic GBM cohort. The fact that the two groups were matched for other variables known to influence outcomes indicates that differences between the groups were solely due to the presence of a cyst. We found a median actuarial survival time of 18.7 months (95% CI 4–33.4 months) in patients with cystic GBMs, compared with 14.4 months (95% CI 11.7–17 months) in the matched noncystic GBM group. In the cystic GBM group, 45% of patients survived for 2 years, compared with only 15% in the noncystic GBM group (p = 0.1). The strong trend toward improved survival in patients with cystic GBMs is noteworthy (Fig. 2), despite the limited statistical power of this study.

Most importantly, our analysis demonstrated that patients with cystic GBMs had a statistically significant improvement in recurrence-free survival compared with patients with noncystic GBMs. Specifically, the 1-year progression-free survival rate was 45%, and 38% of patients did not experience tumor recurrence or regrowth as of 2 years after surgery. In contrast, progressive tumor recurrence was shown in patients in the noncystic GBM group, and at 2 years only 9% of cases exhibited no sign of recurrence (log-rank test, p = 0.04). This difference could not be explained by differences in other variables between the groups because the matching process was expected to rule these out. Moreover, most tumors in both groups (including those located in eloquent brain) were removed by gross-total resection. Our finding is particularly noteworthy because the difference observed was statistically significant, despite the small number of patients in each group. Thus, patients with cystic GBMs had more favorable outcomes in survi-

FIG. 3. Graph showing freedom from recurrent disease in patients with cystic GBMs and those with noncystic GBMs. The differences between the two groups’ curves are significant (p = 0.04).

al and time to tumor recurrence than patients with noncystic GBMs.

The cause of cyst formation remains unclear. One hypothesis that has been posed to explain formation of these large cysts is malignant transformation of a previously undiagnosed cystic low-grade glioma.8,17,18,23 Glioblastomas multiforme are thought to arise from low-grade astrocytomas in approximately 20% of cases.2,17,18,23 These “secondary” GBMs tend to occur in younger patients (median 45 years) who have a long history of seizures, and the lesions have different genetic and molecular patterns compared with so-called “primary” or de novo GBMs. The secondary GBMs appear to differ in prognosis and response to therapy.18 If cystic GBMs develop from low-grade cystic gliomas, then we would expect the clinical features of patients in our study to be similar to features of patients with secondary gliomas. In our series, however, the patients’ clinical characteristics of age (mean 55 years), time of onset of seizures, and other clinical manifestations did not differ from those seen in large series of patients with GBMs that previously had been published and were not the same as features of secondary GBM (long preoperative clinical history, mean age < 41 years).13,19,21,31,32,35,38,40 Therefore, we did not find clinical data to support the hypothesis of malignant transformation. Other hypotheses suggested to explain the presence of a cyst in GBMs include necrotic degeneration of tumor tissue, central hemorrhage with subsequent liquefaction, entrapment of adjacent cerebrospinal fluid space, or a blood–brain barrier disruption.1,14,26,28 Our study was not formulated to evaluate these theories. Further studies, in which molecular, clinical, and neuroimaging analyses are used, are necessary to address the cause of cyst formation in GBMs.

The propensity of glial tumors to invade normal brain is one of their hallmarks. The GBM typically invades adjacent brain tissue, but the biochemical determinants of this process are not completely defined. Frequently, this invasion occurs in the white fiber tracts, along blood vessels, by subependymal dissemination, and through the subpial space.3,7.
Tumor infiltration is thought to account for early postoperative recurrence and disease progression despite aggressive resection. Our finding of longer survival and a lower tumor recurrence rate in the cystic GBM group compared with the noncystic GBM group suggests that cystic tumors may be more circumscribed lesions, with a different pattern of invasiveness. Whole-brain histological mapping studies of untreated GBMs, which have been performed by Burger and colleagues, have demonstrated that GBMs vary greatly in the extent of parenchymal invasion, which in some instances consists of only a narrow rim of infiltrating tumor. In our histological studies of specimens in which the relationship of the cyst wall to the brain could be analyzed, we have demonstrated that a cystic GBM appears to have a relatively narrow pericystic rim of glioma, with limited infiltration of the surrounding neuropil (Fig. 4). This indicates that cystic GBMs may be less infiltrative than noncystic GBMs. This would predispose patients with cystic GBMs to have an improved time to recurrence and a longer overall survival time after surgery. Nevertheless, because of the limited numbers of cases in this analysis, we must interpret this finding with caution. Clearly, prospective morphological studies specifically designed to address this issue in cases of cystic GBMs are needed.

Conclusions

Patients with GBMs that contain a large cystic component had more favorable outcomes in survival and time to tumor recurrence than their counterparts with noncystic GBMs. We believe that the biological behavior of circumscribed cystic GBM lesions is different from that of noncystic GBMs. To our knowledge, this is the first study in which this biological variable was correlated with outcome. Future studies should include a larger series of patients who will be prospectively reviewed (including molecular and genetic determinants) to define the usefulness of this variable as a prognostic indicator.

References


Fig. 4. Photomicrographs demonstrating the cyst wall of a cystic GBM. A: The cyst lumen (L) is bordered by a cuff of GBM (GM) measuring only 0.5 cm in maximal thickness. B: At a higher magnification, limited infiltration of the surrounding brain parenchyma (P) is seen (arrows indicate tumor interface with surrounding neuropil). H & E, original magnification × 20 (A) and × 40 (B).
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